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SYNTHETIC AND ^{13}CMR STUDIES ON CYATHINS

by

© Dale E. Ward

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1979

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

SYNTHETIC AND ^{13}CMR STUDIES ON CYATHINS

submitted by Dale E. Ward in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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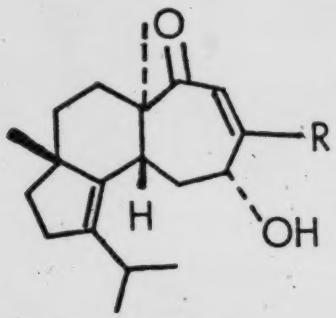
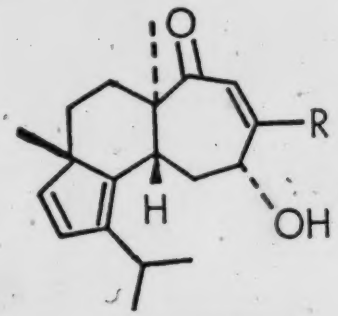
ABSTRACT

The first chapter of the thesis deals with the transformation of the major diterpenoid metabolite of C. helenae, cyathin A_3 (1), into the more biologically active metabolites cyathin B_3 (2) and cyathin C_3 (3).



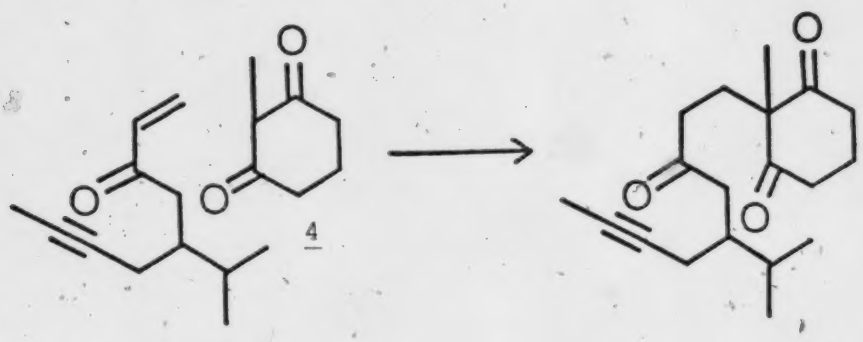
1 R=CH_2OH
2 R=CHO



3 R=CHO

In the second chapter preliminary work in the investigation of the biosynthesis of cyathin diterpenoids is presented. This involved the complete assignment of the resonances in the carbon-13 nuclear magnetic resonance (^{13}CMR) spectrum of various cyathins and their derivatives.

The third chapter deals with an unsuccessful approach to the synthesis of cyathins. This approach envisioned the use of a Robinson annulation of 2-methyl-1,3-cyclohexanedione (4) with the enone 5 to provide the key intermediate 7. However we were unable to induce the aldol cyclization of the Michael adduct



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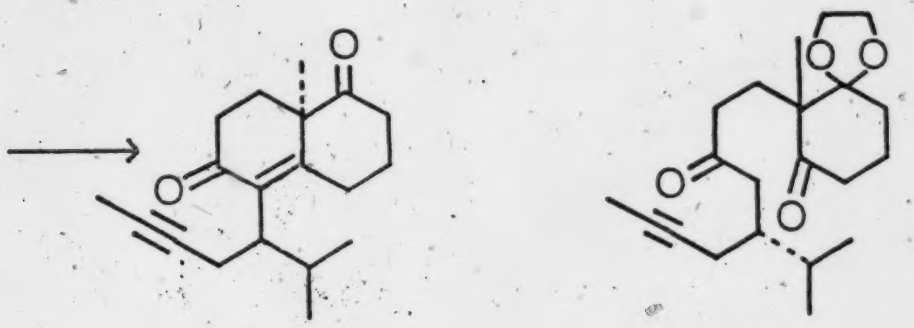
6 or its ethylene acetal derivative 8 and this approach was abandoned.



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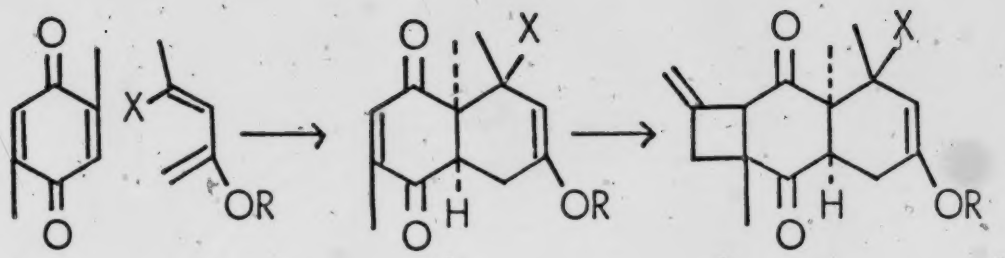
Finally the fourth chapter of the thesis describes a Diels-Alder approach to the synthesis of cyathins. This approach has led to the synthesis of 11 in 30% overall yield in 5 steps from the quinone 9 via the trione 10. The tricyclic 11 possesses the desired stereochemistry about the ring junctions as well as functional groups which should allow for further elaboration into cyathin diterpenoids.



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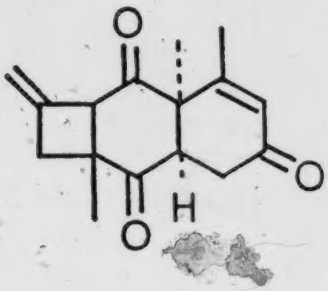

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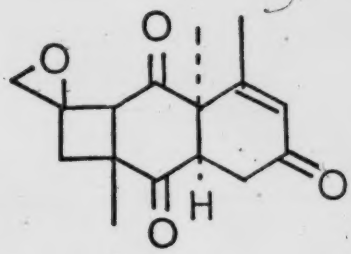

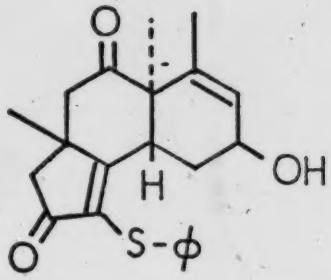

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INTRODUCTION

In 1965, while on a field trip in the Rocky Mountains, H.J. Brodie discovered a new bird's nest fungus of the genus Cyathus.[1] The family to which these fungi belong is Nidulariaceae (derived from nidula, meaning little nest) and are so named because the fruit bodies which contain lentil-shaped spores resemble a miniature bird's nest. Brodie designated this new species as C. helenae and was able to culture it on liquid media.[2] Later it was discovered that an ethyl acetate extract of the culture broth afforded a mixture that showed antibiotic activity.[2,3] This mixture was then investigated by Ayer and co-workers in an effort to isolate the active components.

Repetitive chromatography of this mixture or "cyathin complex" as it was designated, led to the isolation of two compounds named cyathin A_3 and allocyathin B_3. A thorough examination of the chemical and spectral properties of these compounds and their derivatives led Ayer and Taube[5] to propose structures 1 and 2 respectively. This was confirmed by an X-ray crystallographic study of cyathin A_3.[6] Subsequent work has shown that cyathins B_3 and C_3[7] and neoallocyathin A_4,[8] further metabolites of C. helenae, have structures 3, 4, and 5 respectively.

Further studies of other species of the genus Cyathus

have also yielded metabolites bearing the cyathin skeleton: cyafrins A_4 (6), B_4 (7), A_5 (8), and allocyafrin B_4 (9) from C. africanus,[9] four cyathatriols (10), cyathin B_2 (11) and allocyathin B_2 (12) from C. earlei;[10] striatins A (13), B (14), and C (15) from C. striatus.[11]

The cyathins and related compounds constitute a family of diterpenes that was previously unknown.* Because of the novel skeleton possessed by these compounds we became interested in the investigation of their laboratory synthesis as well as the nature of their biosynthesis. This thesis details preliminary studies towards these two objectives.

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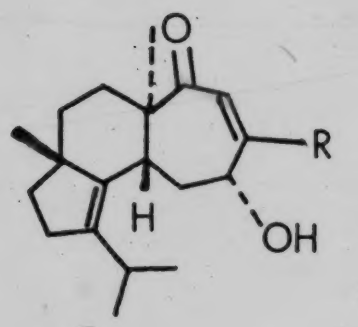
* For an introduction to the various families of terpenes, see A.A. Newman "Chemistry of Terpenes and Terpenoids," Academic Press, New York, N.Y., 1972.



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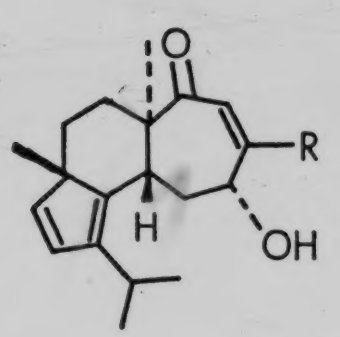
3 R=CHO



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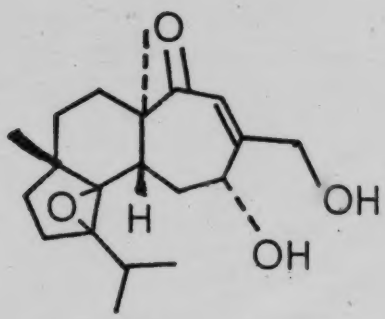

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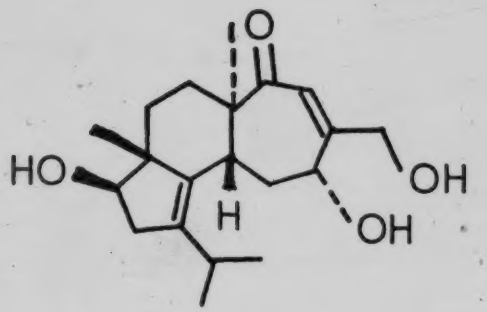

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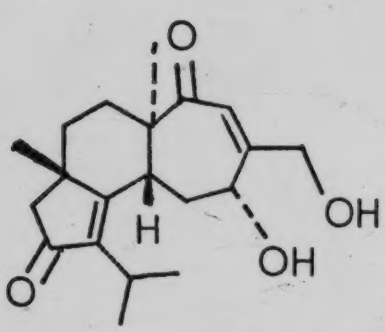

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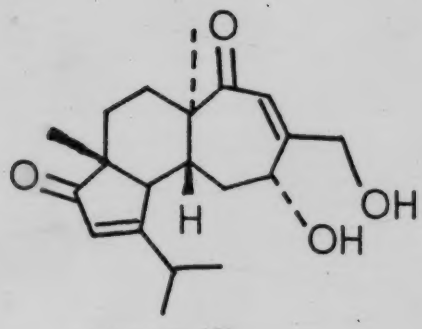

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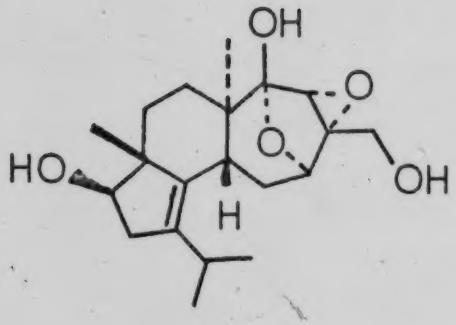

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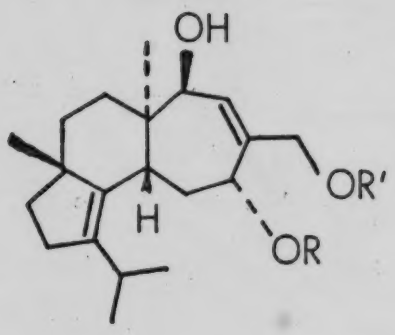
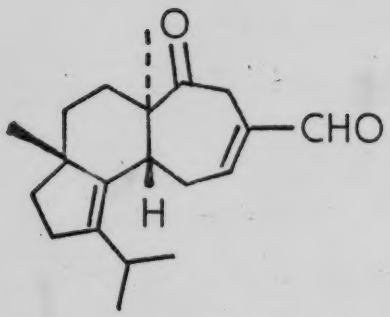


10a R,R'=H 10c R=H, R'=Ac

10b R,R'=Ac 10d R'=H, R=Ac



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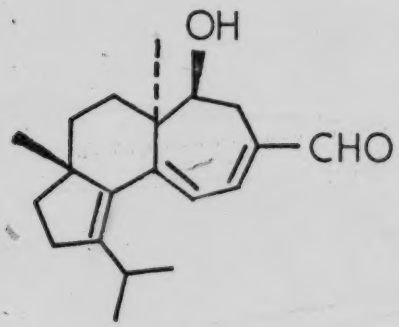

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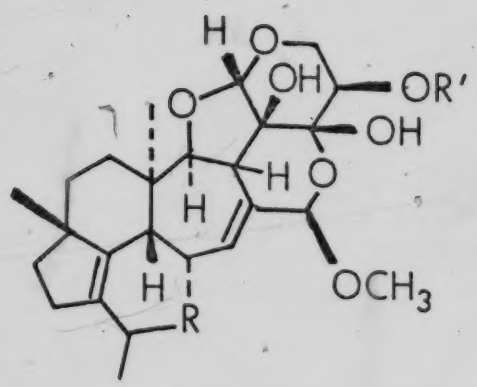


13 R,R'=H

14 R=H, R'=Ac

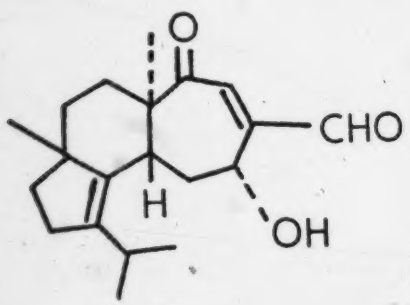
15 R=OH, R'=Ac

CHAPTER I

SOME CHEMICAL CORRELATIONS AMONG THE CYATHINS*

Results and Discussion

The total crude metabolites isolated from C. helenae showed significant antimicrobial activity.[4] Further testing indicated that the components mainly responsible for this activity are the α,β-unsaturated aldehydes cyathin B_3 (1) and cyathin C_3 (2).[8] Since the major



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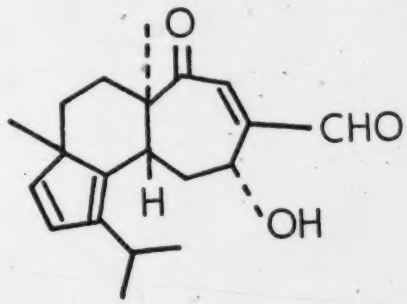

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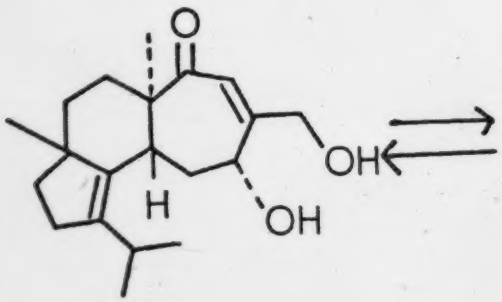
component of the crude mixture of metabolites is cyathin A_3 (3), it became desirable to develop methods for the conversion of 3 into 1 and 2.



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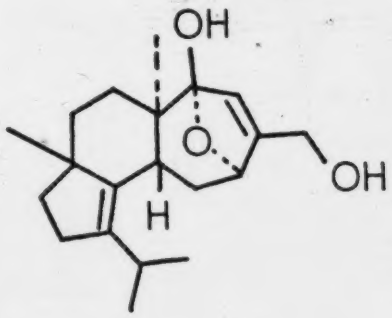

3b

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* Some of this work has been published.[8]

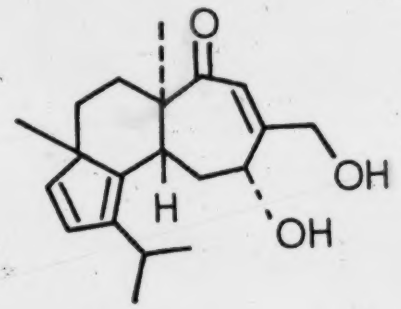
The transformation of cyathin A_3 into cyathin B_3 involves the selective oxidation of the primary allylic alcohol function to an aldehyde function. In solution cyathin A_3 exists as a mixture of the hydroxy ketone form 3a and the tautomeric internal hemiacetal 3b. By taking advantage of the internal protection of the secondary allylic alcohol function in 3b, we felt selective oxidation of the primary alcohol would be possible without resorting to a protection-oxidation-deprotection scheme.

Solution infrared spectra of cyathin A_3 were obtained in $CHCl_3$, CH_2Cl_2, methanol, and ether. Whereas the carbonyl absorption was significant in the spectra determined in the former solvents, the spectrum determined in ether showed very weak absorption in this region. These results indicate that in ether cyathin A_3 has a greater propensity to exist in the internal hemiacetal form 3b.

Oxidation of cyathin A_3 (3) with activated manganese dioxide[12] in ether gave as the only product cyathin B_3 (1) in greater than 80% yield.

The transformation of cyathin A_3 into cyathin C_3 involves the introduction of a double bond in the A ring to form a diene system as well as the selective oxidation outlined in the previous (3 → 1) conversion. Because of the sensitivity of the unsaturated aldehyde function both to oxidation and Michael-type additions,[7] we chose

to first form the diene system, then perform the oxidation to the aldehyde, i.e., to proceed *via* allocyathin B_3 (4) rather than *via* cyathin B_3 (1).



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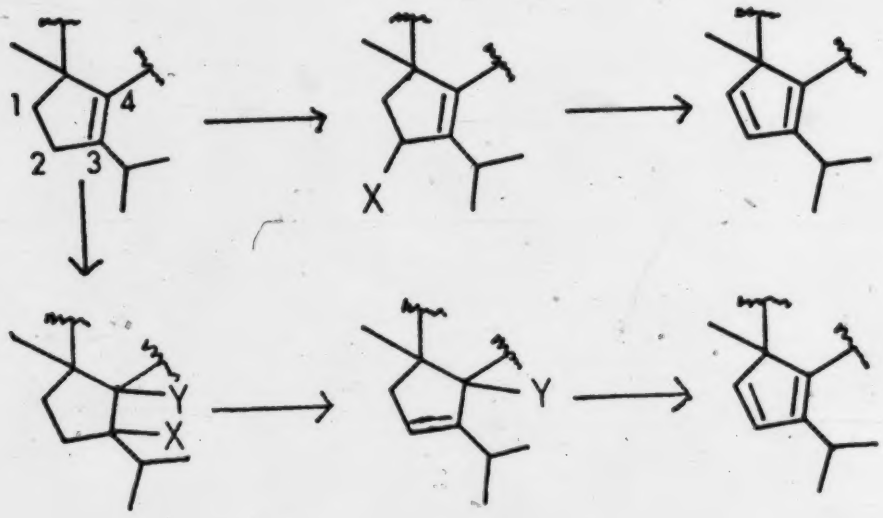
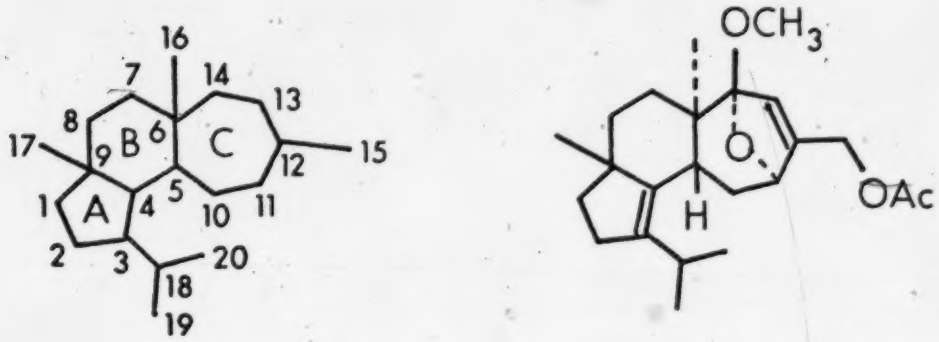
The creation of a 1,3 diene system should be possible by utilizing the 3,4 double bond in either an allylic substitution (at C-2), elimination sequence or, alternatively, by an addition (at C-3,4), double elimination (2,3 followed by 1,4) sequence (see Scheme 1).



Scheme 1. Possible sequences for preparation of A ring diene

Since the C-12,13 double bond in O-acetylcyathin A_3 methyl acetal (5) should be unreactive towards allylic substitution and this function would be difficult to protect against addition reactions, we chose to investigate the allylic substitution, elimination sequence.



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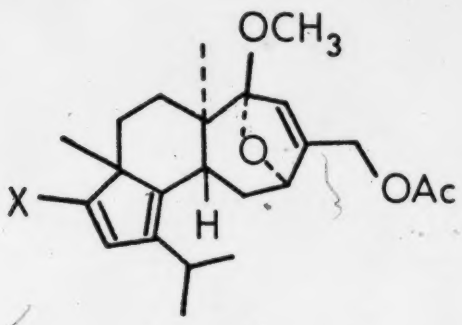
Although tertiary centers react preferentially to secondary centers, we felt that allylic substitution at C-2 would be possible since C-18 should be unreactive due to the steric inhibition of resonance[13] caused by the severe interaction of the isopropyl methyls with the C-10 hydrogens, and C-5 is sterically hindered.

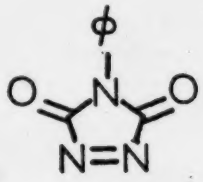
Treatment of 5 with N-bromosuccinimide (1 equiv.) in refluxing CCl_4 in the presence of a trace of benzoyl peroxide gave a mixture of two products along with starting material in the ratio of ca. 1:1:1. The two products could be separated from starting material by preparative thick layer chromatography (PTLC) using 10% $AgNO_3$-silica gel. Although the products could not themselves be separated, chemical and spectral evidence

(ms, nmr) indicated that one component was O-acetylallocyathin B_3 methyl acetal (6) and the other was its C-1 bromo derivative (7).* The mass spectrum of the mixture



6 X=H

7 X=Br



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was very similar to that of 6[14] with an additional peak at m/e 450 corresponding to a molecular formula of $C_{23}H_{31}O_4{}^{79}Br$. Similarly the ^{1}Hmr spectrum of the mixture closely resembled that of 6[14] with the main difference being a new singlet at δ 6.35 superimposed on the AB quartet for the olefinic hydrogens at C-1,2. In addition both products gave a Diels-Alder adduct with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (8)[15] indicating the presence of an s-cis diene.

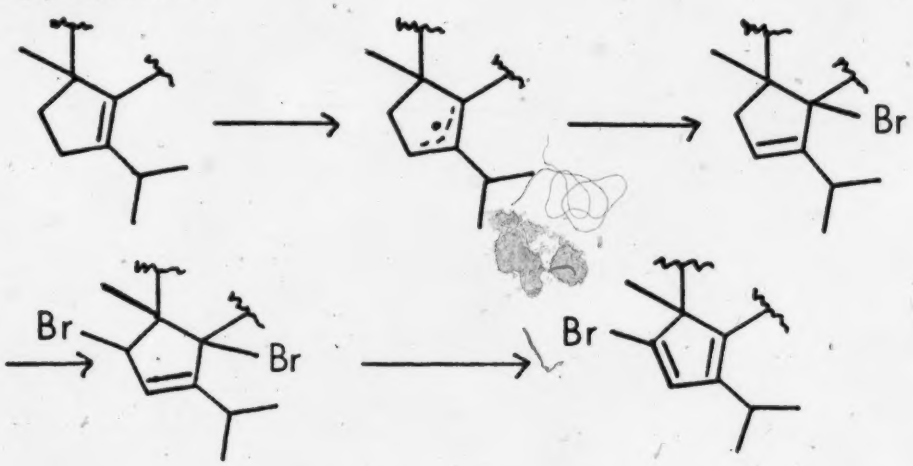
In an attempt to stop the reaction at the monobromination stage, i.e. before the elimination of HBr, 5 was

---

* The assignment of the bromine at C-1 is based on mechanistic considerations as well as ^{13}Cmr studies (for a detailed account see Chapter 2).

treated with N-bromosuccinimide (1 equiv.) in CCl_4 at room temperature in the presence of tertiary butyl hydroperoxide and Cu(II)laurate.* However the major product was the bromo diene 7. Since we could not stop the reaction at the allylic bromide stage and since reduction of the bromo diene would also yield an allocyathin B_3 derivative we decided to see whether the bromo diene 7 could be made the exclusive product of the reaction.

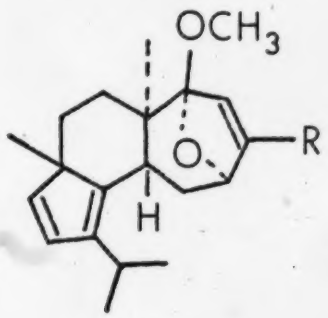
Treatment of 5 with N-bromosuccinimide (2.1 equiv.) in refluxing CCl_4 in the presence of benzoyl peroxide gave in 82% yield after PTLC the bromodiene 7. The formation of 7 can be accounted for by a mechanism involving a double allylic bromination followed by a 1,4 elimination of HBr (see Scheme 2) for which there is some precedence.[16]



Scheme 2. Mechanism for formation of bromodiene 7.

* tBuOOH/Cu(II)laurate is a redox couple that acts as a radical initiator at room temperature.[16]

Treatment of 7 with a large excess of the reagent prepared from $Li(OMe)_3AlH$ and CuI ("$LiCuH_2$")[17] in tetrahydrofuran (THF) gave in 76% yield after PTLC allocyathin B_3 methyl acetal (8) identical (nmr, ir, ms, tlc) with an authentic sample.

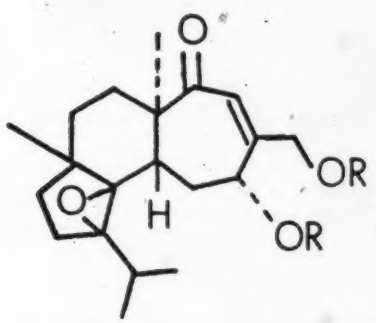


8 R=CH_2OH

9 R=CHO

Acid catalyzed hydrolysis of 8 gave allocyathin B_3 (4). Oxidation of 8 with MnO_2 in ether gave cyathin C_3 methyl acetal (9) which could be hydrolyzed with aqueous perchloric acid in THF to give cyathin C_3 (2). Alternatively allocyathin B_3 could be oxidized with MnO_2 in ether in a similar fashion as described previously for cyathin A_3, to give cyathin C_3.

For the sake of completeness we also converted cyathin A_3 into neoallocyathin A_4 (10). Thus 0,0-diacetylcyathin A_3 was oxidized with m-chloroperbenzoic acid to give 11 which was deacetylated with K_2CO_3 in methanol to give 10.



10 R=H

11 R=Ac

In conclusion cyathins B_3, C_3, allocyathin B_3, and neoallocyathin A_4 are now available synthetically from cyathin A_3.

Experimental

Mass spectra were recorded on an A.E.I. MS-50 mass spectrometer and are reported as m/e (relative intensity). Unless diagnostically significant only peaks at least 20% as intense as the base peak are reported. Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating spectrophotometer. Proton magnetic resonance spectra were measured on a Varian HA-100 spectrometer with TMS as the internal standard.

Preparative thick layer chromatography (PTLC) was carried out on 1.0 mm layers of silica gel G (E. Merck, Darmstadt) containing 1% electronic phosphor (General Electric, Cleveland) and materials were detected by uv (254 nm) or by spraying with 30% H_2SO_4 and charring.

Cyathin A_3 was isolated as described previously.[5b] O-acetylcyathin A_3 methyl acetal (5) as well as O,O-diacetylcyathin A_3 were prepared as previously reported.[5b] All solvents were reagent grade and distilled prior to use. Skellysolve B refers to Skelly Oil Company light petroleum b.p. 62-70°.

Cyathin B_3 (1) from Cyathin A_3 (3a ⇄ 3b).

Cyathin A_3 (103 mg) was dissolved in ether (40 ml) and activated manganese dioxide[12] (750 mg) was added. The mixture was stirred at room temperature for 2 hr, then filtered and the filtrate evaporated to yield a

colorless oil (80 mg, 80%) which solidified on standing. The product was identified as cyathin B_3 by comparison (ir, ms, tlc) with an authentic sample.

O-Acetyl-1-bromoallocyathin B_3 methyl acetal (7).

O-Acetylcyathin A_3 methyl acetal (5, 75 mg) was dissolved in CCl_4 (8 ml) and N-bromosuccinimide (75 mg) and a trace of benzoyl peroxide (~1 mg) was added. The mixture was stirred under reflux for 3 hr, then filtered, evaporated, and the residue subjected to PTLC (silica gel, Skellysolve B:acetone (3:1)) to give 7 (75 mg, 82%) as an oil which was used in the next step without further purification.

IR (neat): 1732 cm^{-1}

^{1}HMR ($CDCl_3$) δ: 0.82 (s, 3 H) and 0.97 (s, 3 H) (C-16 and C-17 methyls), 1.04 (d, J = 7 Hz, 3 H) and 1.10 (d, J = 7 Hz, 3 H) isopropyl methyls, 2.09 (s, 3 H, acetyl methyl), 3.21 (s, 3 H, ketal methyl), 4.77 (m, 3 H, C-11 and C-15 H's), 6.14 (m, 1 H, C-13 H), 6.35 (s, 1 H, C-2H).

MS: m/e calcd. for $C_{23}H_{31}O_4{}^{79}Br$: 450.1405; found: 450.1399; calcd. for $C_{23}H_{31}O_4{}^{81}Br$: 452.1385; found: 452.1389.

Allocyathin B_3 methyl acetal 8 from 7.

Lithium trimethoxyaluminum hydride (3 ml, 1.04 M) in tetrahydrofuran (THF) was added dropwise to cuprous

iodide (290 mg) in THF (0.6 ml) at 0° under nitrogen. After a few drops had been added, the mixture became yellowish-brown and viscous. Further THF (~0.5 ml) was added to allow efficient stirring. This process was repeated until all of the $Li(OCH_3)_3AlH$ solution had been added. The mixture was then stirred at 0° for 15 min to give a dark brown solution. The bromo diene 7 (80 mg) in THF (0.5 ml) was added. After stirring for 5 min at 0° the solution was allowed to warm to room temperature and was stirred for 8 hr, then CH_3OH (1 ml) was added dropwise, followed by H_2O (0.1 ml). The solution was diluted with ether, filtered through Celite and washed successively with saturated NH_4Cl solution and brine. Drying ($MgSO_4$) and evaporation of the solvents left an oil which was purified by PTLC (silica gel, Skellysolve B:acetone (3:1)) to give allocyathin B_3 methyl acetal (8, 45 mg, 76%), identical (tlc, ir, nmr, ms) with an authentic sample.

Cyathin C_3 methyl acetal (9) from 8.

Allocyathin B_3 methyl acetal (8, 20 mg) in ether (2 ml) was stirred with activated manganese dioxide[12] (100 mg) at room temperature for 30 hr. Filtration and evaporation of solvent gave cyathin C_3 methyl acetal (9, 18 mg, 90%), identical with an authentic sample.

Allocyathin B_3 (4) from 8.

The acetal 8 (40 mg) was dissolved in THF (4 ml) and 1 N aq. perchloric acid (0.5 ml) was added and the solution was stirred at room temperature for 5 days after which time tlc showed only the desired 4. The solution was diluted with saturated aq. $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the solvent gave allocyathin B_3 (4, 32 mg, 84%) as an oil, identical (tlc, ir, ms) with authentic material. Oxidation of 4 with MnO_2-ether as described above yielded cyathin C_3 (2).

O,O-Diacetylneoallocyathin A_4 (11).

O,O-Diacetylcyathin A_3 (100 mg) in CH_2Cl_2 (5 ml) was treated with m-chloroperbenzoic acid (55 mg) at room temperature for 30 min, then the solution was washed (aq. $NaHCO_3$, H_2O) and evaporated to give O,O-diacetylneoallocyathin A_4 (11) as an oil (93 mg, 89%).

IR (neat): 1748, 1660 cm^{-1};

^{1}HMR ($CDCl_3$) δ: 1.05 (s, 3 H, C-16 CH_3), 1.06 (d, 3 H, J = 7 Hz), and 1.07 (d, 3 H, J = 7 Hz) isopropyl methyls, 1.28 (s, 3 H, C-17 CH_3), 2.02 and 2.11 (acetyl methyls), 4.65 (m, 2 H, C-15 H's), 5.39 (m, 1 H, C-11 H), 6.13 (bs, 1 H, C-13 H).

MS: m/e calcd. for $C_{24}H_{34}O_6$: 418.2355; found: 418.2355.

Neoallocyathin A_4 (10).

O,O-Diacetylneoallocyathin A_4 (40 mg) was dissolved

in CH_3OH (4 ml) and K_2CO_3 (20 mg) was added. After 30 min tlc indicated that the reaction was completed. The mixture was diluted with H_2O and extracted with $CHCl_3$ to give neoallocyathin A_4 (10) as an oil.

IR (neat): 3400 br, 1642 br.

^{1}HMR ($CDCl_3$) δ: 1.01 (s, 3 H, C-16 CH_3), 1.06 (d, 3 H, J = 7) and 1.10 (d, 3 H, J = 7) isopropyl methyls, 1.24 (s, 3 H, C-17 CH_3), 4.0-4.5 (m, 3 H, C-11 and C-15 H's), 6.03 (bs, 1 H, C-13 H).

MS: m/e calcd. for $C_{20}H_{30}O_4$: 334.2144; found: 334.2138.

CHAPTER II

^{13}CMR OF CYATHINS*

Discussion

In recent years carbon-13 nmr has become a powerful tool in biosynthetic investigations.[19] It is the only nondestructive method capable of directly determining the location and concentration of isotopic labels in a metabolite. Simply stated the technique involves incubation with a suitably labeled biogenetic precursor followed by isolation of the desired metabolite and detection of the location of the precursor by the enhanced absorption in the carbon-13 nmr spectrum. By using multiply labeled precursors, spin-spin coupling effects can provide direct evidence for the incorporation of intact biogenetic units as well as for biosynthetic processes involving bond formation and cleavage.

Because of the novel skeleton of the cyathins we became interested in investigating their biosynthesis. The molecular formulas of the cyathins as well as the fact that they contain five C-methyl group equivalents suggest that they belong to the diterpenoid group of natural products.[20] The natural precursor of diterpenoids is considered to be geranylgeranyl pyrophosphate[21] which is ultimately derived from acetate. Ayer and Taube[5b]

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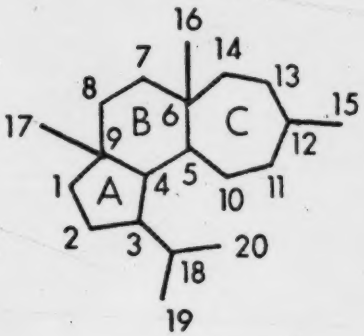
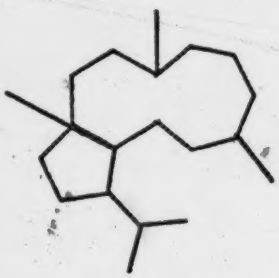
* Some of this work has been published.[18]

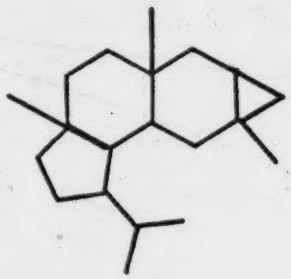
have proposed a biosynthetic pathway to cyathins (see Scheme 1). Recent reports on the isolation of new natural products possessing the somewhat related skeletons dolabellane[22] and verrucosane[23] suggest an alternative pathway (see Scheme 2).



Cyathane

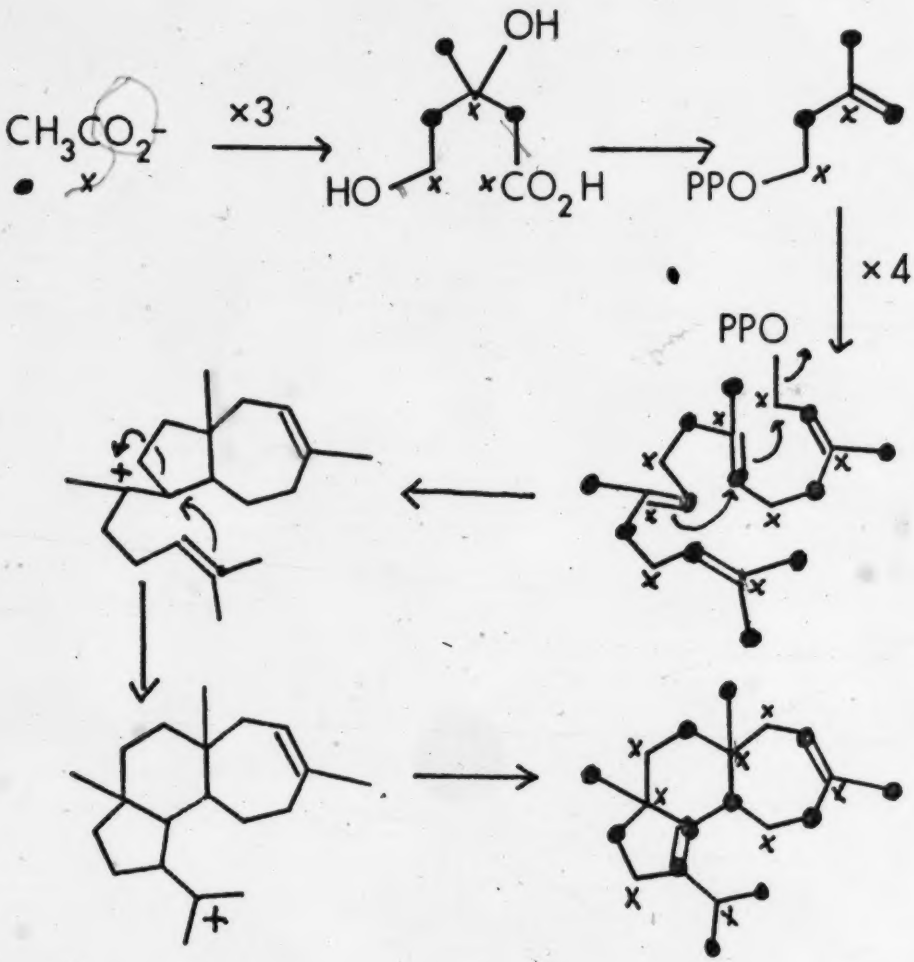


Dollabellane

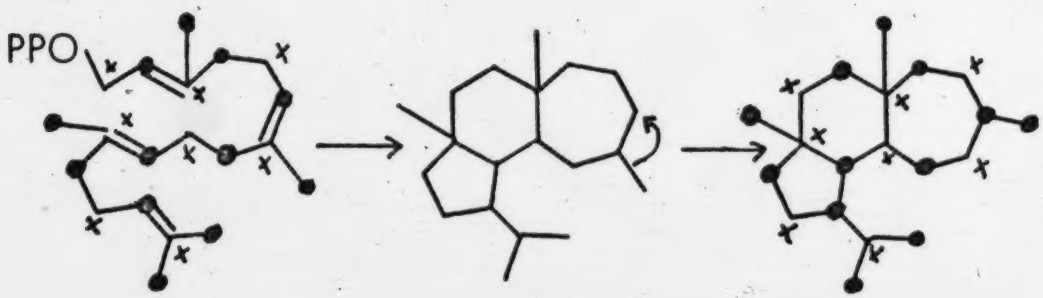


Verrucosane

These two pathways are readily distinguished by carbon-13 nmr since incorporation of [1-^{13}C]- or [2-^{13}C]-acetate into a cyathin would lead to different labeling patterns (see Schemes 1 and 2). For example, incorporation of [1-^{13}C]acetate into a cyathin *via* Scheme 1 would lead to enhancement of the resonances attributed to carbons 2, 6, 8, 9, 10, 12, 14, and 18 in the carbon-13 nmr spectrum, whereas incorporation *via* Scheme 2 would lead to enhanced signals for carbons 2, 5, 6, 8, 9, 11, 13, and 18. Moreover, incorporation of [1,2-^{13}C]acetate could provide evidence for the carbon-carbon bond breaking processes involved in these two pathways.



Scheme 1. Proposed biogenesis of cyathin

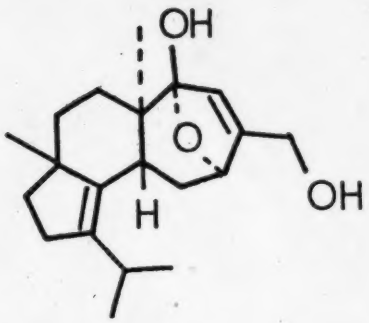


Scheme 2. Alternative biogenesis of cyathin

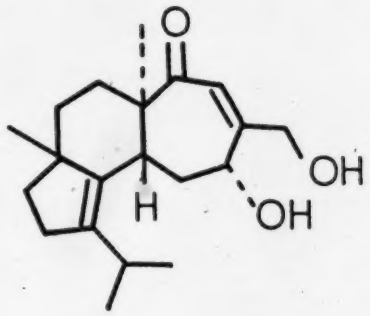
Naturally, the prerequisite for obtaining this type of biosynthetic information is the unequivocal assignment of the carbon-13 resonances. Thus as a prelude to the investigation of the biosynthesis of cyathins as well as to aid in assigning structures to newly discovered members of this class of diterpenoids we undertook a study of the carbon-13 nmr spectra of representative compounds.

Results

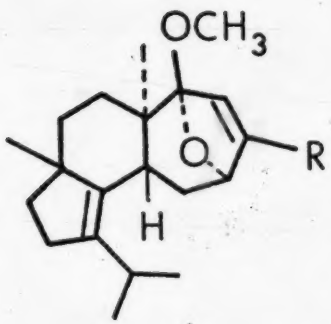
The ^{13}C chemical shifts of 1-9 are summarized in Table 1. The ^{13}C spectrum of 1 resulted in 40 distinct carbon resonances due to the slow interchange (on the nmr time scale) between hemiacetal and hydroxy ketone forms, which are represented by structures 1a and 1b, respectively. The complete analysis of this spectrum proved to be difficult so a number of derivatives of 1, in which the molecular framework is "locked" in either the open (hydroxy ketone) or closed (acetal) form, were prepared and their ^{13}Cmr spectra obtained. A comparison of the ^{13}C shieldings of 1 with those obtained for 3 and 4 reveals a one to one correspondence of the ^{13}C resonances (except for carbons α and β to a substituent change, e.g., an -OH replaced by an -OAc group) of both closed forms (1a and 4) and both open forms (1b and 3). That is, the ^{13}C spectrum obtained from the tautomeric



1a



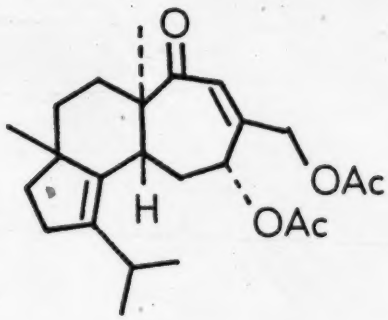
1b



2 R=CH_2OAc

4 R=CH_2OH

5 R=CHO



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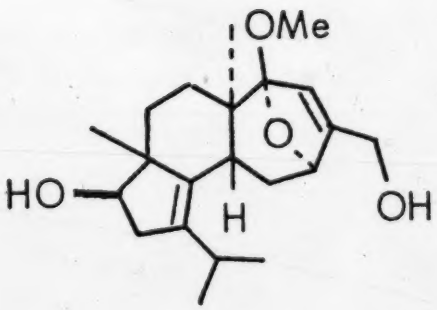

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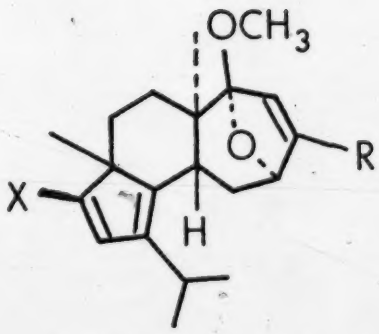


7 X=H, R=CH_2OH

8 X=H, R=CHO

9 X=Br, R=CH_2OH

Table 1. Carbon-13 Chemical Shifts[a] of Several Cyathins

Carbon	1a	1b	2	3	4	5	6	7	8	9
1	40.1	37.9	40.0	38.0(0.2)[b]	40.0(0.4)	40.0	81.9	144.3(0.3)	144.3	133.5
2	28.9	28.6	28.7	28.8(0.3)	28.8(0.3)	28.8	35.3	127.9(0.2)	128.0	128.5
3[d]	139.5	140.5	139.3	140.7(0.6)	139.3(0.7)	140.2	136.7	142.5(0.6)	141.5	143.3[c]
4	136.6	136.3	136.5	135.5(0.4)	136.5(0.7)	135.5	136.3	141.0(0.6)	141.4	141.6
5	39.8	38.5	39.6	38.7(1.2)	39.8(0.6)	39.7	40.7	39.3(1.3)	39.2	40.1
6	42.2	54.8	42.2	54.3(1.3)	42.2(1.5)	42.0	41.8	44.6	44.2	45.3
7	30.5	34.6	30.3	34.7(1.9)	30.3(1.2)	30.6	29.9	29.1(0.9)	29.4	28.8
8	37.3	36.1	37.2	36.2(0.6)	37.2(0.6)	37.1	36.3	31.4(0.5)	31.2	31.5
9	48.3	49.4	48.2	49.3(0.4)	48.2(0.6)	48.1	49.0	54.1(0.4)	54.0	55.7
10	26.8	35.6	26.9	31.7(1.2)	27.0(1.7)	26.7	27.4	25.8(1.4)	25.6	25.9
11	78.9	71.9	78.9	72.0(1.9)	78.4(2.5)	76.8	78.6	78.4(1.0)	76.8	78.6
12	147.9	153.9	143.2	143.4(3.2)	148.5(1.5)	148.6	149.3	148.4(1.2)	148.4	143.5
13	123.2	126.0	127.7	127.4(3.3)	123.9(3.7)	147.9	123.2	123.8(2.7)	147.8	127.4
14	110.6	211.0	114.4	208.7	114.4(3.2)	114.7	114.7	114.7	114.7	114.3

continued.....

Table 1 (continued)

Carbon	1a	1b	2	3	4	5	6	7	8	9
15	58.4	64.8	60.0	64.7(2.4)	59.0(13.0)	186.7	58.1	58.6(10.0)	186.5	59.7
16	11.6	15.5	11.9	14.8(1.7)	11.9(1.1)	11.8	11.6	11.8(0.8)	11.8	11.8
17	24.3	24.1	24.0	24.0(0.3)	24.2(0.5)	24.0	16.4	20.6(0.5)	20.7	20.5
18	26.5	27.1	26.4	27.2(0.4)	26.4(0.3)	26.4	26.6	25.8(0.3)	25.7	25.9
19[d]	22.4	22.0	22.3	21.7(0.2)	22.4(0.2)	22.3	21.7	22.8(0.2)	22.7	22.7
20	21.3	21.5	21.4	21.7(0.2)	21.3(0.1)	21.2	20.4	22.7(0.2)	22.7	22.7
$-OCH_3$			51.1		51.0(1.4)	51.7	50.0	50.9(1.2)	51.7	51.0
$-CO_2-$			170.4	170.1						170.2
				169.8						
$-O_2C\underline{C}H_3$			20.7	20.8(1.5)						20.8
				20.8(1.6)						

[a]All values from TMS. Accurate to ±0.1 ppm. [b]Values in parenthesis indicate $Eu(fod)_3$ induced shifts. [c]May be interchanged with C-12. [d]Signals for C-3 and C-4 may be interchanged, as may those for C-19 and C-20.

mixture (1a and 1b) can be "synthesized" by combining the spectra obtained for 3 and 4. Thus, assignments of the ^{13}C resonances of 3 and 4, along with the other derivatives, leads to the separate assignments of 1a and 1b.

Assignments of the ^{13}C resonances were made in the following manner. The carbon shieldings may be grouped into approximately four regions:[24] 1) those corresponding to carbonyl carbons at ~190 ppm; 2) those to olefinic carbons at ~130 ppm; 3) those to carbons bound to oxygen at ~60 ppm; and 4) those to saturated carbons at ~30 ppm. The carbonyl carbon resonances were readily assigned. In the second group, proton selective (for 2, 3, and 4) and off-resonance decoupling (for 2 to 5) unambiguously distinguished the resonances of C-13 from those due to C-3, C-4 and C-12. The shielding of C-13 is decreased by ~20 ppm upon introduction of -CHO (5 and 8) in place of $-CH_2OH$ (4, 6, and 7) or $-CH_2OAc$ (2, 3, and 9) as expected.[24] The resonances due to C-12 may be separated from those due to C-3 and C-4 by additivity (β acetyl in 2 vs β hydroxy in 4; 2 → 4 for C-12, ~+5 ppm). For 7, 8, and 9 two additional signals due to C-1 and C-2 appear in this region and the more shielded carbon is assigned to C-2.[25]

The third group, C-11, C-14, C-15, and the $-OCH_3$ were assigned unambiguously based on their characteristic

shieldings and multiplicities in the off-resonance spectrum.

In the fourth group, the resonances due to C-6 and C-9 were separated on the basis of their multiplicities obtained in the off-resonance spectrum. Little change in shielding is expected for C-9 upon ring closure (3 → 2), and on this basis the resonances of C-6 and C-9 were assigned. Selective proton decoupling for 2, 3, and 4 unambiguously assigned the resonance due to C-18; the remaining methine carbon in this region is due to C-5. The shieldings of these carbons should remain relatively constant for this series of compounds. Selective proton irradiation on 2, 3, and 4 allowed the assignment of C-2; again no change in shielding is expected for this carbon in 1-5.

Turning to the methyl carbons, C-16 is expected to be the most shielded due to its crowded environment. It also shows the largest shift on ring closure (i.e., 3 → 2). C-17 is assigned to the least shielded of the methyl resonances because of the higher degree of α and β branching. The acetyl methyls in 2 and 3 were assigned by selective proton decoupling.

The remaining methylene carbons in 1-5 (C-1, C-7, C-8, and C-10) were assigned in the following manner. Examination of Table 1 shows good agreement of the resonances for 3 and 4 when compared to those obtained

for the tautomeric mixture, 1a and 1b. The only discrepancy in this region occurs at δ 31.7 for 3 when compared to δ 35.6 for 1b. The only expected change in shielding should occur at C-10 for which a β-hydroxyl group in 1b is replaced by a β-acetyl group in 3 (for C-10; 1b → 3, -5 ppm[24]). Changing from the open form (e.g., 1b or 3) to the closed form (e.g. 1a or 4) causes two of the methylene carbons to become slightly less shielded (~1 ppm) and the other two to become more shielded (~-5 ppm). In 4, one of the protons of C-10 is in a syn-axial orientation with respect to C-16; thus, C-10 is assigned to the most shielded of the methylene carbons. The other methylene carbons which might be affected by internal acetal formation would be C-7 or C-8; the close approach of the C-10 proton to those of C-16 could result in a large perturbation on C-8. Alternatively the shielding of C-7 could be influenced, either electronically or sterically, depending upon the functionality at C-14.

To explore this point further a $Eu(fod)_3$ shift study was undertaken to distinguish between C-1, C-7 and C-8 (as well as to confirm some of the other assignments) in 3, 4, and 7 and the results are summarized in Table 1. It is well established that lanthanide induced shifts are quantitatively reproduced by the pseudo contact or dipolar shielding term given by:[26] $\Delta_i = C(1-3\cos^2\theta_i)/R_i^3$

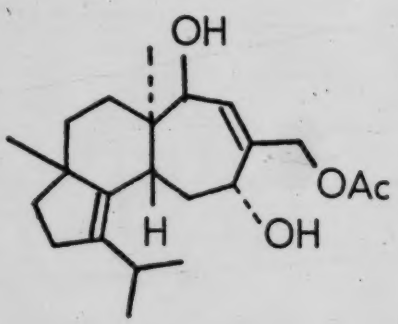
where Δ_i is the induced shift at nucleus i, C is a constant at a given temperature, $(1-3\cos^2\theta_i)$ is an orientational factor and R_i is the distance of the shift reagent to nucleus i. The equation is known to break down for carbons α and β to the complexing site (generally a Lewis base) because of the presence of a contact interaction contribution to the shielding.[26] Thus, for 3, 4, and 7 the shielding of C-7 is expected to be more sensitive to the addition of $Eu(fod)_3$ than C-8 which in turn should be more sensitive than C-1 and the signals were assigned accordingly. The $Eu(fod)_3$ induced shifts for the other carbons in 3, 4, and 7 are consistent with the previous assignments.

The conversion of cyathin A_3 (1) into allocyathin B_3 (hydroxy ketone form of acetal 7) via the monobromo compound 9 is described in the previous chapter. The method of preparation of 10 did not allow us to determine whether the bromine is located at C-1 or C-2. Examination of the ^{13}Cmr spectrum of 9 (Table 1) shows that C-1 is strongly shielded in 9 (relative to 7 and 8) which is consistent with the location of the bromine at C-1.[27]

Conclusion

Now that we had succeeded in assigning the carbon-13 spectrum of various cyathins we attempted to incorporate labeled acetate. Several attempts to grow C. helenae on

still culture in the presence of various amounts of sodium acetate failed to yield the desired metabolites. Similar experiments with C. africanus were also unsuccessful. However using C. earlei, where the metabolites are isolated from the mycelium extract as opposed to the broth extract, Ayer and Lee have recently been successful in incorporating [1-^{13}C]acetate into 15-O-acetylcyathatriol (10).



10

Analysis of the carbon-13 nmr spectrum of 10 shows enhancement for the resonances attributable to carbons 2, 6, 8, 9, 10, 12, 14, and 18. These results are consistent with the biogenesis outlined in Scheme 1. Further work attempting to incorporate [2-^{13}C] and [1,2-^{13}C]acetate is now in progress.

Experimental

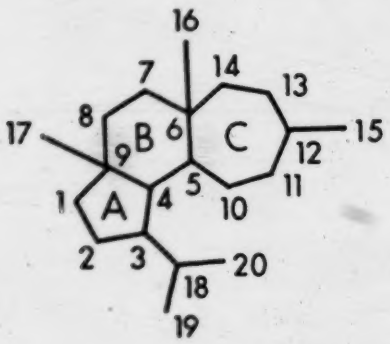
The ^{13}Cmr spectra were obtained on natural abundance samples at a concentration of approximately 0.2 to 0.5 M in $CDCl_3$-5% TMS at a frequency of 22.63 MHz (Bruker HFX-90) and at 15.08 MHz (Bruker WP-60) in 10 mm sample tubes. For those samples (7, 8 and 9) of limited quantity, a 1.7 mm microinsert was used. Cyclohexane (~ 2μℓ) was used as the internal reference in these cases and the data converted to the TMS scale ($\delta_{C_6H_{12}}$ = 27.7). All the chemical shifts obtained in this manner appeared to be too high by an average of 0.9 ppm, consequently the reported values in Table 1 have been corrected. For the shift reagent study, $Eu(fod)_3$-d_{10} (Norell Chemical Company, Inc.) was added stepwise, up to 0.0168 g of reagent to 0.020 g of 3, 0.192 g of reagent to 0.130 g of 4, and 0.075 g of reagent to 0.050 g of 7. ^{1}Hmr spectra were obtained in $CDCl_3$ on a Varian HA-100. Cyathin A_3 (1a ≠ 1b) was isolated as previously described.[5b] The preparation of 2, 3 and 4 has been described.[5b] The preparation of 5, 7, 8 and 9 is described in the previous chapter as well as in reference 8. Compound 6 was prepared by Dr. T. Yoshida from cyafrin A_4 as previously described.[9]

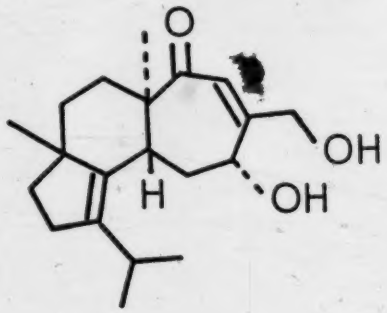
CHAPTER III

A ROBINSON ANNULATION APPROACH TO THE SYNTHESIS OF CYATHINS*

Results and Discussion

In developing a synthetic strategy for the cyathins let us first examine the structure of a typical member of this class, cyathin A_3 (1). This is a reasonable





1

starting point in that 1 is probably the simplest member of the cyathins and moreover it would be relatively straight forward to transform 1 into various other members of this class.‡

Obviously any proposed strategy must take into account the existing dissymmetric centers at carbons 5, 6, 9, and 11. Of these four centers we felt that construction of the carbons at the ring junctions (5,6,9) in the proper orientation would be the most difficult

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* Some of this work has been published.[29]

‡ For some examples of such transformations see Chapter I.

problem. Needless to say there are a great number of synthons that may be envisioned as leading to the cyathin skeleton.* These are only limited by our lack of knowledge and imagination.

The starting point in our strategy was based on our feeling that the problem would be greatly simplified if the C ring was initially introduced as a six-membered ring which at a later stage could be ring expanded and appropriately functionalized. In order to substantiate this idea we undertook a model study with 2,2-dimethylcyclohexanone (2) (see Scheme 1).

Treatment of 2 with ethyldiazoacetate in the presence of boron trifluoride etherate[30] gave after hydrolysis and decarboxylation (15% H_2SO_4 1↓) the desired 2,2-dimethylcycloheptanone (4) in 66% overall yield. The ketone 4 was dehydrogenated *via* the corresponding α-phenylselenide to the enone 5 according to Reich's[31] procedure. Formation of the ethylene ketal in the usual way proceeded with double bond migration as expected.[32] In the ^{1}Hmr spectrum of 6 simultaneous irradiation of the olefinic protons (δ 5.48) caused a doublet of doublets at δ 2.37 to collapse to a broad singlet confirming the position of the double bond. Hydroxylation of 6 with osmium tetroxide in pyridine/THF gave after workup and chromatography

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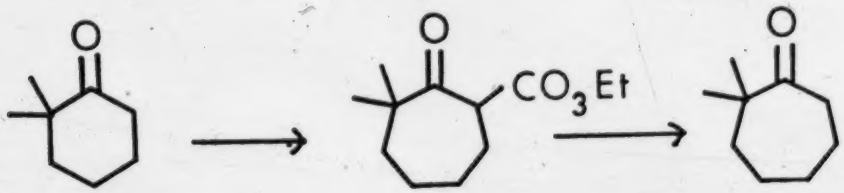
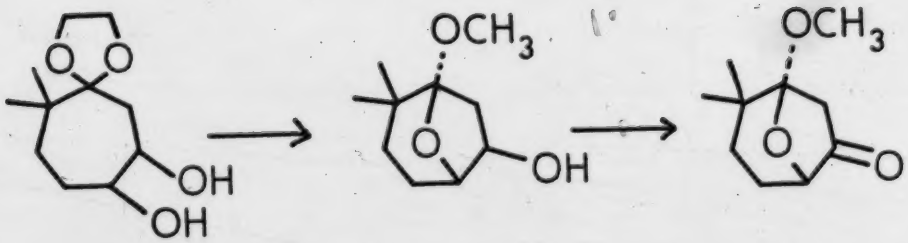
* For a discussion of various possible synthons see ref. 28.

Scheme 1. Model study for ring expansion



2 3 4

5 6

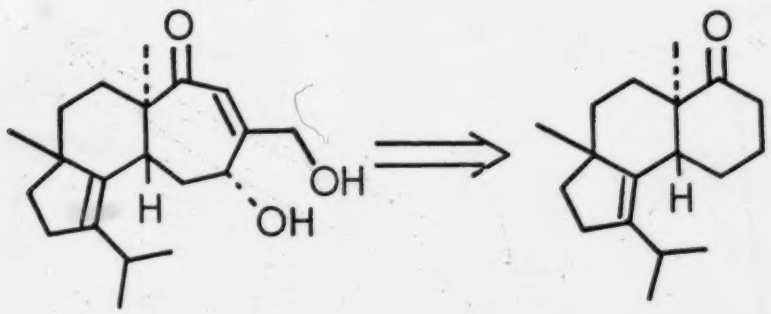


7 8 9

10 11

the desired diol 7 in 32% overall yield from 4. Treatment of 7 with methanol-HCl gave the internal methyl acetal 8, a reaction patterned after a similar reaction employed by Johnson[33] in an A-homosteroid system. Jones' oxidation of 8 gave the bicyclic ketone 9 which was treated with dimethylsulfonium methylide according to Corey's[34] procedure to give the spiroepoxide 10 in 47% overall yield from the diol 7 after chromatography. Treatment of 10 with aqueous acid in acetone failed to produce isolatable quantities of the desired 11. Although the quantity of the epoxide 10 available precluded optimization of this final reaction, we felt that the results in hand were encouraging enough to proceed via a six-membered C ring synthon in our overall synthetic strategy.

Bearing this principle in mind the synthetic problem now reduces to the construction of a 5-6-6 tricyclic intermediate such as 12. This intermediate sharply focuses

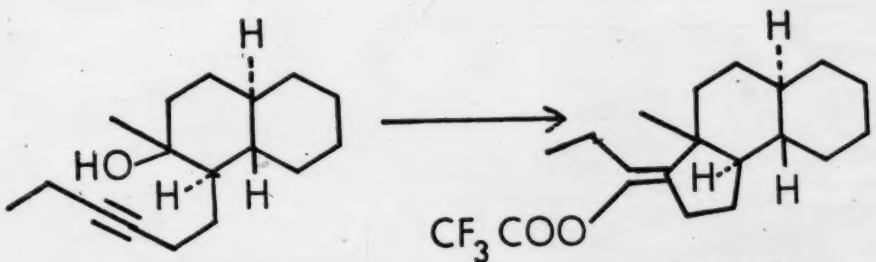


1 12

on the problem of assembling the carbon atoms at the ring junctions in the proper configuration. The relative

stereochemistry of the ring system in 12 bears an analogy to the B, C and D rings of steroids as well as to the C, D and E rings of pentacyclic triterpenoids. Thus we examined the literature on the synthesis of these classes of compounds in an effort to find methods for the construction of 12 which might be expected to give the desired stereochemistry.*

Lansbury[35] has described the stereoselective cyclization of the acetylenic alcohol 13 to the tricyclic compound 14. We felt that compound 15 should undergo



13 14

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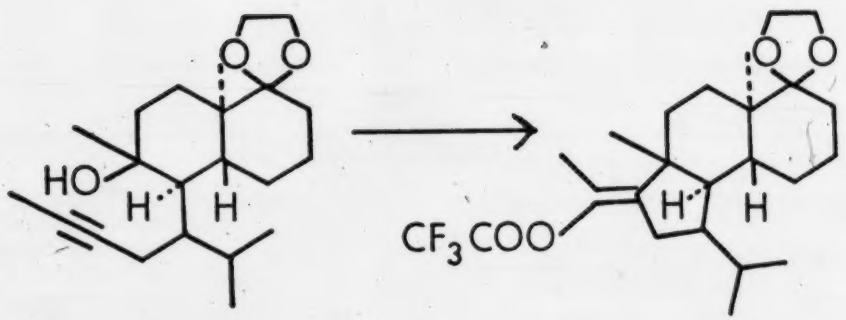
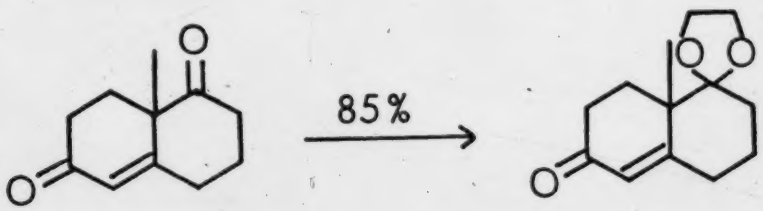
* For a review on the synthesis of steroids see, R.T. Blickenstaff, A.C. Ghosh, G.C. Wolf, "Total Synthesis of Steroids," Academic Press, New York, N.Y., 1974. For a review on the synthesis of triterpenes see, J.W. ApSimon, J.W. Hooper, in "Total Synthesis of Natural Products," edited by J.W. ApSimon, J. Wiley Inc., New York, N.Y., 1973, pp. 559-640.



15 16

a similar reaction to give 16 which could be transformed to the desired 12.

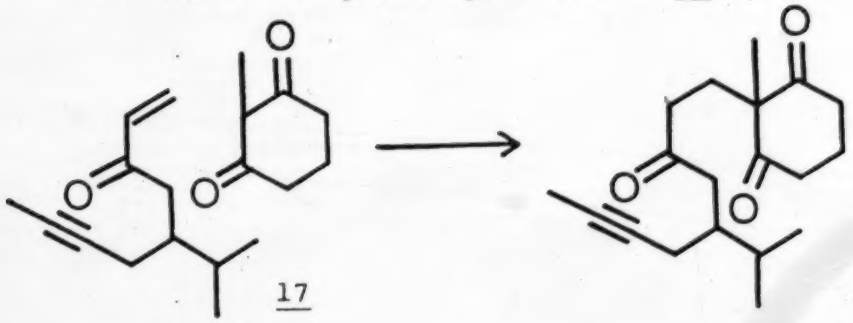
The synthesis of 15 can be envisioned to arise (see Scheme 2) via a Robinson annulation[36] utilizing the readily available 2-methyl-1,3-cyclohexanedione (17) along with the enone 16. Michael addition followed by aldol cyclization should give rise to the enedione 19. The selective protection of the saturated ketone function in 19 should be straight forward in analogy to the Wieland-Miesher ketone 22.[37] A dissolving metal reduction



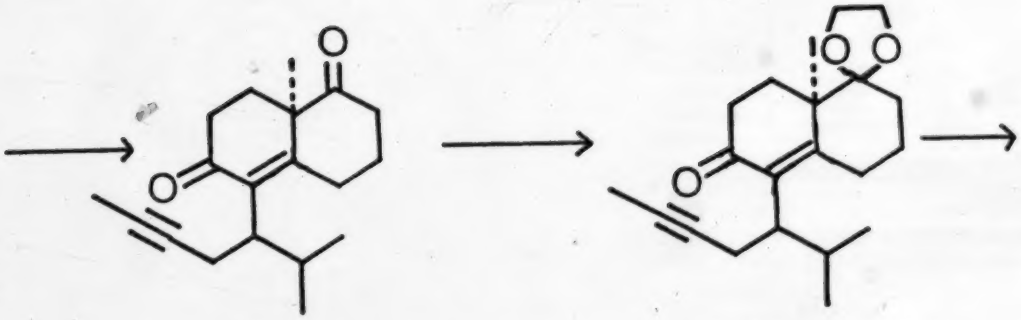
22 23

of the resulting enone 20 should lead to the thermodynamically more stable product 21[38] with the required trans

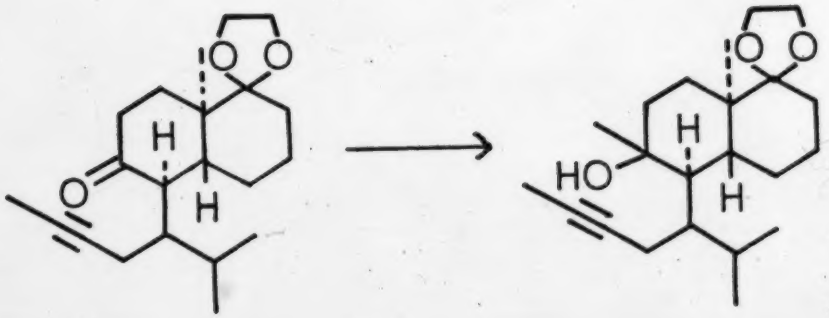
Scheme 2. Proposed synthesis of 15



16 17 18



19 20

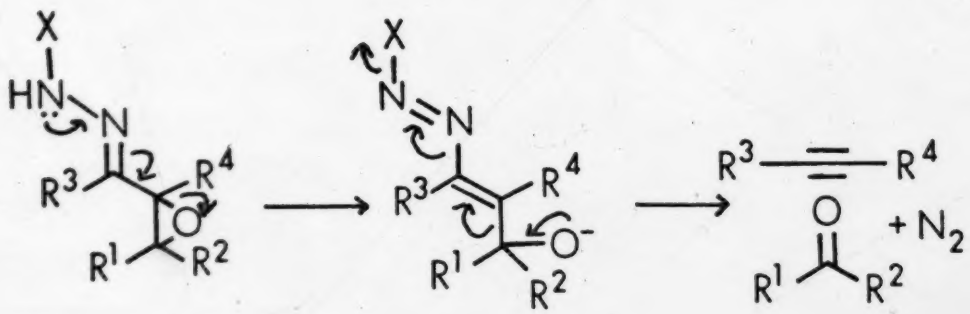


21 15

ring junction.* Addition of methyllithium or alternatively methylmagnesium bromide to 21 would then give the desired acetylenic alcohol 15.

This route to 15 was especially attractive due to recent developments[39] in asymmetric induction in the Robinson annulation of cyclic 1,3-diones using optically active amino acids in the aldol cyclization step. Utilizing this procedure such a route could conceivably lead to optically active cyathins. Thus we set out to prepare the required enone 16.

The presence of both an acetylene and a carbonyl function in 16 prompted us to consider the use of an Eschenmoser cleavage reaction in its preparation. It is reported[40] that certain α,β-epoxyhydrazones, prepared from the corresponding α,β-epoxyketones, undergo a fragmentation reaction producing both an acetylene and a carbonyl fragment.

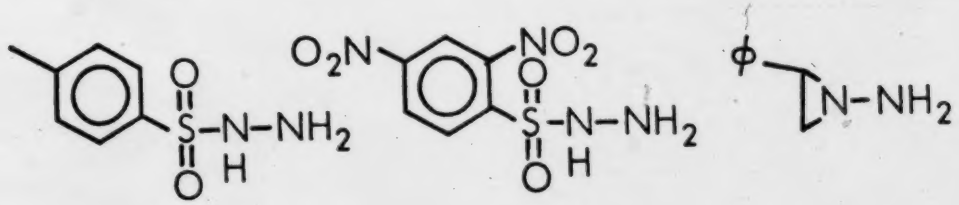


* Lansbury[35] has demonstrated that this type of reduction can be performed in the presence of an acetylene function.

We felt that the enone 16 could be prepared from the corresponding aldehyde by addition of vinyllithium followed by oxidation of the resulting allylic alcohol.* Construction of the appropriate acetylenic aldehyde by an Eschenmoser fragmentation would require an α,β-epoxyhydrazone which could be derived from the readily available monoterpene carvone (see Scheme 3).

Treatment of (+)-carvone (24) with basic hydrogen peroxide gave the epoxyketone 25 which after hydrogenation over platinum oxide provided 26 in 83% overall yield.

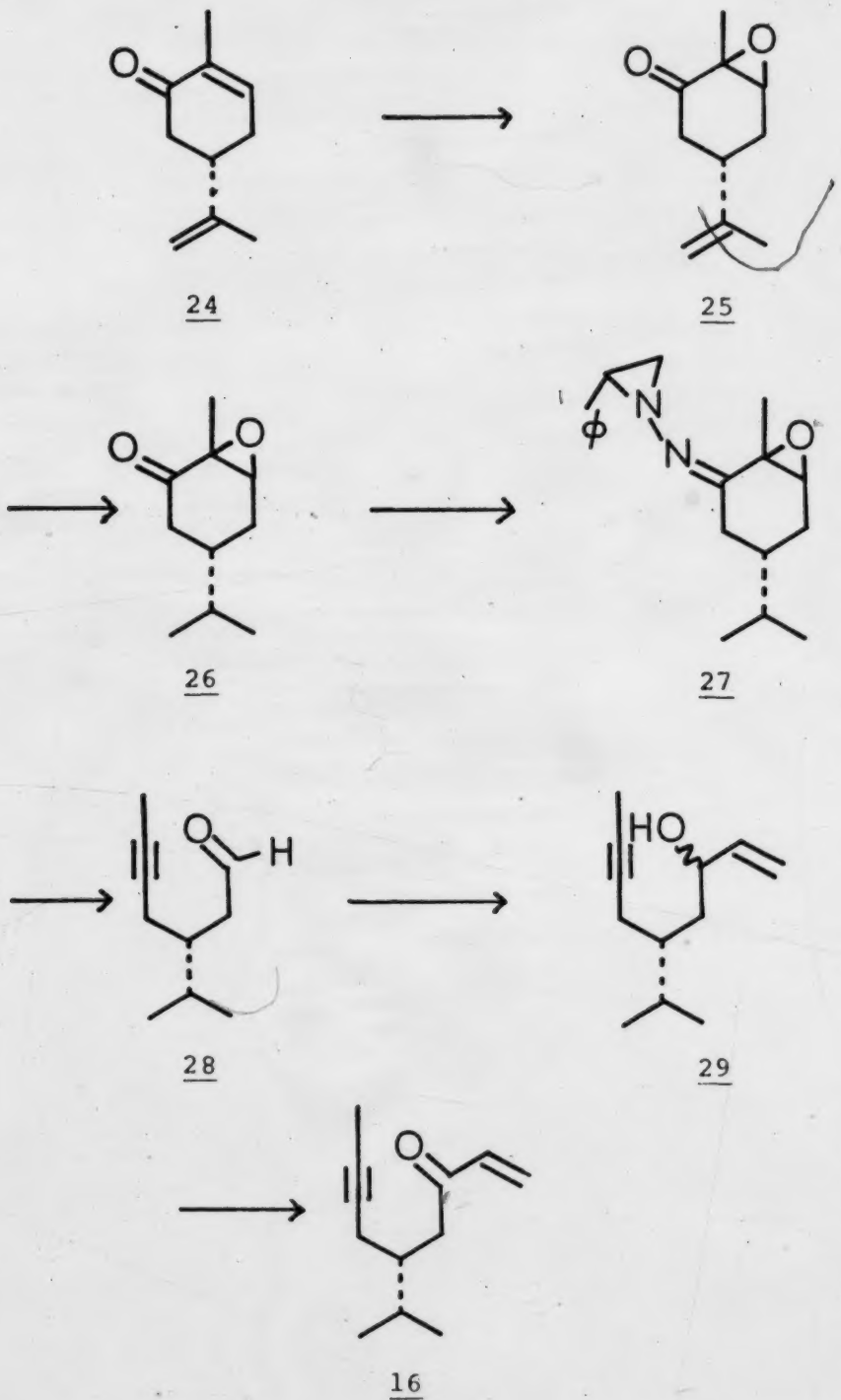
The reagent normally employed to effect fragmentation of epoxyketones is p-toluenesulfonylhydrazine (30). However it is reported[40,41] that this reagent works poorly for α,β-epoxyketones containing a β-hydrogen, i.e., compounds leading to acetylenic aldehydes rather than acetylenic ketones. Other reagents have been developed to overcome this difficulty: 2,4-dinitrobenzenesulfonylhydrazine (31)[41] and 1-amino-2-phenylaziridine (32).[40]



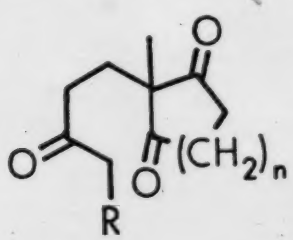
30 31 32

* For an example of this type of transformation see, S. Danishefsky and P. Cain, J. Org. Chem., 39, 2925 (1974).

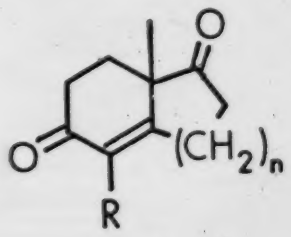
Scheme 3. Synthesis of enone 16



Initial attempts to effect fragmentation of 26 using 31 proved unsuccessful. However reduced pressure pyrolysis of the hydrazone 27, readily prepared from the epoxyketone 26 and the aziridine 32, afforded after distillation the desired acetylenic aldehyde 28 in 70% yield. Addition of vinyllithium to 28 at -78°C gave a diastereomeric mixture of alcohols which after Jones' oxidation provided the desired enone 16 in 36% overall yield from carvone (24). Treatment of 16 with 2-methyl-1,3-cyclohexanedione (17) in refluxing dimethoxyethane in the presence of a catalytic amount of sodium hydride produced the Michael adduct 18. With the desired trione in hand we attempted to effect an aldol cyclization to produce optically active 19.



33



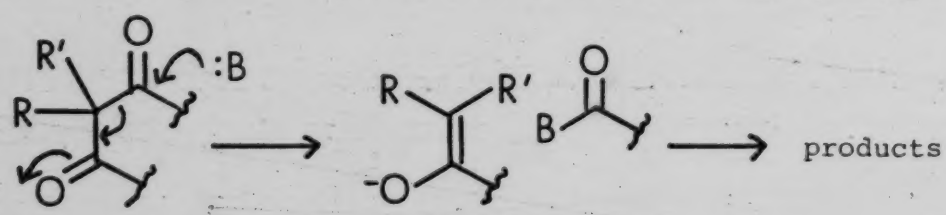
34

n = 1,2

It has been shown[39b] that in these types of cyclizations (33 → 34) the use of S amino acids lead to the S configuration while R amino acids give the R antipode. As well it seems that when R ≠ H, phenylalanine is the most effective catalyst.[39c] Since in 19 the desired

configuration at the ring junction is R, we attempted to effect the cyclization of 18 in the presence of R-phenylalanine under conditions that had proved successful in other cases[39] (see Table 1). However even after prolonged reaction time only starting material could be isolated. Thus we turned to more "normal" conditions to effect cyclization,[36] but here again we were unable to induce ring closure with all conditions yielding either recovered starting material or intractable tars (see Table 1).

The use of base catalysis (e.g. HO^- or RO^-) to induce ring closure of 18 was precluded due to the efficacious cleavage of 2,2-dialkyl-1,3-diones such as 18 under these conditions.[36] We felt that if one of the carbonyl



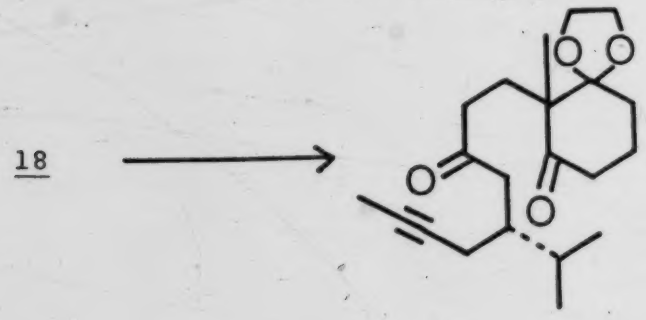
groups in the 1,3-dione system could be protected this facile cleavage reaction would be obviated.

The trione 18 was treated with 2-methyl-2-ethyl-1,3-dioxolan in benzene solution in the presence of HCl to give a mono ethylene acetal derivative in good yield.[42] Examination of the spectral data for this derivative suggested that the acetal was derived from a cyclic

Table 1. Attempts to Cyclize 18

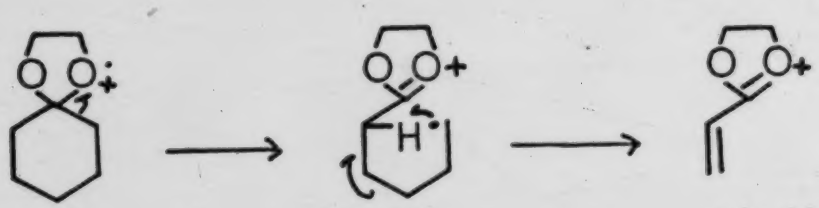
	Reaction Conditions	Time	Result
1.	D-phenylalanine (1 eq.), 1N $HClO_4$ (.25-10 eq.), CH_3CN, 80°C.	5 days	no reaction
2.	D-phenylalanine (1 eq.), HOAc, 115°C.	3 days	no reaction
3.	D-phenylalanine (1 eq.), DMF, 25°C.	4 days	no reaction
4.	D-phenylalanine (1 eq.), DMF, 80°C.	1 day	DMF reacts with amino acid
5.	pyrrolidine, benzene, 80°C.	4 hrs.	no reaction
6.	pyrrolidine (1 eq.), HOAc (1 eq.), THF, 25°C.	4 days	no reaction
7.	pyrrolidine (1 eq.), HOAc (1 eq.), benzene, 80°C.	2 days	decomposition
8.	pyrrolidine (5 eq.), pTsOH (cat.), benzene, 80°C.	2 days	decomposition
9.	pTsOH (cat.), benzene, 80-140°C.	4 days	no reaction
10.	pTsOH (2.5 eq.), toluene, 110°C.	1 day	decomposition
11.	Et_3N (1 eq.), ϕCO_2H (1 eq.), xylene, 140°C.	3 days	no reaction
12.	Et_3N (1 eq.), HOAc (1 eq.), xylene, 140°C.	3 days	no reaction

ketone. For example the mass spectrum of the product



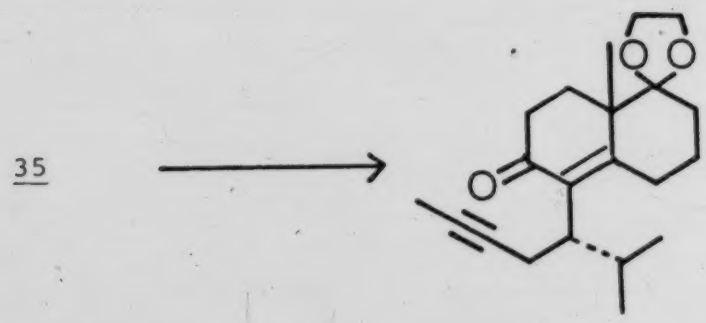
18 → 35

exhibited a base peak at m/e 99 with a molecular formula of $C_5H_7O_2$ characteristic of ethylene acetals of cyclic ketones,[43] thus confirming the structure of 35.



m/e 99

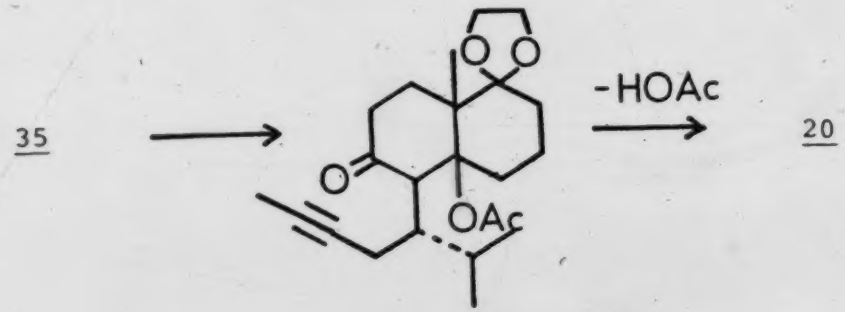
With the desired protected derivative 35 in hand we attempted to effect ring closure to 20 under the influence



35 → 20

of base. Here again however, we were unable to produce the desired 20 under a variety of conditions (see Table 2).

Deslongchamps[44] has described conditions to drive intramolecular aldol condensations to completion by trapping the β-hydroxyketone (ketol) intermediate as its acetate derivative. This is useful in cases where the ketol is highly destabilized relative to its diketone precursor. We felt that this effect could explain our inability to cyclize 35. If the desired ketol intermediate 36 could be trapped as its acetate and the elimination of acetic acid carried out in a subsequent step, then any unfavorable equilibria in the aldol condensation 35 → 20 could be circumvented. However reaction



36

of 35 under Deslongchamps' conditions lead to a mixture of products whose ^{1}Hmr spectrum lacked an acetylenic methyl group (δ 1.75). As a consequence of these results we sought an alternative route to 20.

An Eschenmoser fragmentation of a tricyclic epoxy-

Table 2. Attempts to Cyclize 35

	Conditions	Temp.(°C)	Time (days)	Result
1.	2% KOH-EtOH	78	2	no reaction
2.	1 N NaOMe-MeOH	65	2	no reaction
3.	1 N NaOMe-MeOH	100	2	no reaction
4.	1 N NaOMe-MeOH	150	2	some decomposition
5.	1 N $Mg(OMe)_2$-MeOH	65	2	no reaction
6.	1 N $Mg(OMe)_2$-MeOH	100	2	no reaction
7.	1 N $Mg(OMe)_2$-MeOH	150	2	some decomposition

ketone such as 37 should give rise to 21 (see Scheme 4).* Michael addition of the enedione ester 41 to the enone 42 should lead to 40. Reduction of the double bond should occur from the least hindered side to produce 39 with the desired trans ring juncture. Base catalyzed cyclization with concomitant decarboxylation would give the desired enone 38 which could be oxidized with basic hydrogen peroxide after selective protection of the saturated carbonyl to provide the α,β-epoxyketone 37.

Treatment of 2-methyl-1,3-cyclohexanedione with methyl-3-oxopent-4-enoate[45] in methanol in the presence of a catalytic amount of sodium hydride according to the procedure of Narcarov[46] gave 41 in 50% yield after distillation. However all attempts to effect a Michael addition of 41 to 6-methylhept-4-ene-3-one (42)[47] proved unsuccessful.

Conclusion

In an analysis of a synthetic strategy towards the cyathins involving a Robinson annulation to create the B ring, it is inevitable, regardless of whether a pro A or pro C ring is used as the Michael donor, that the

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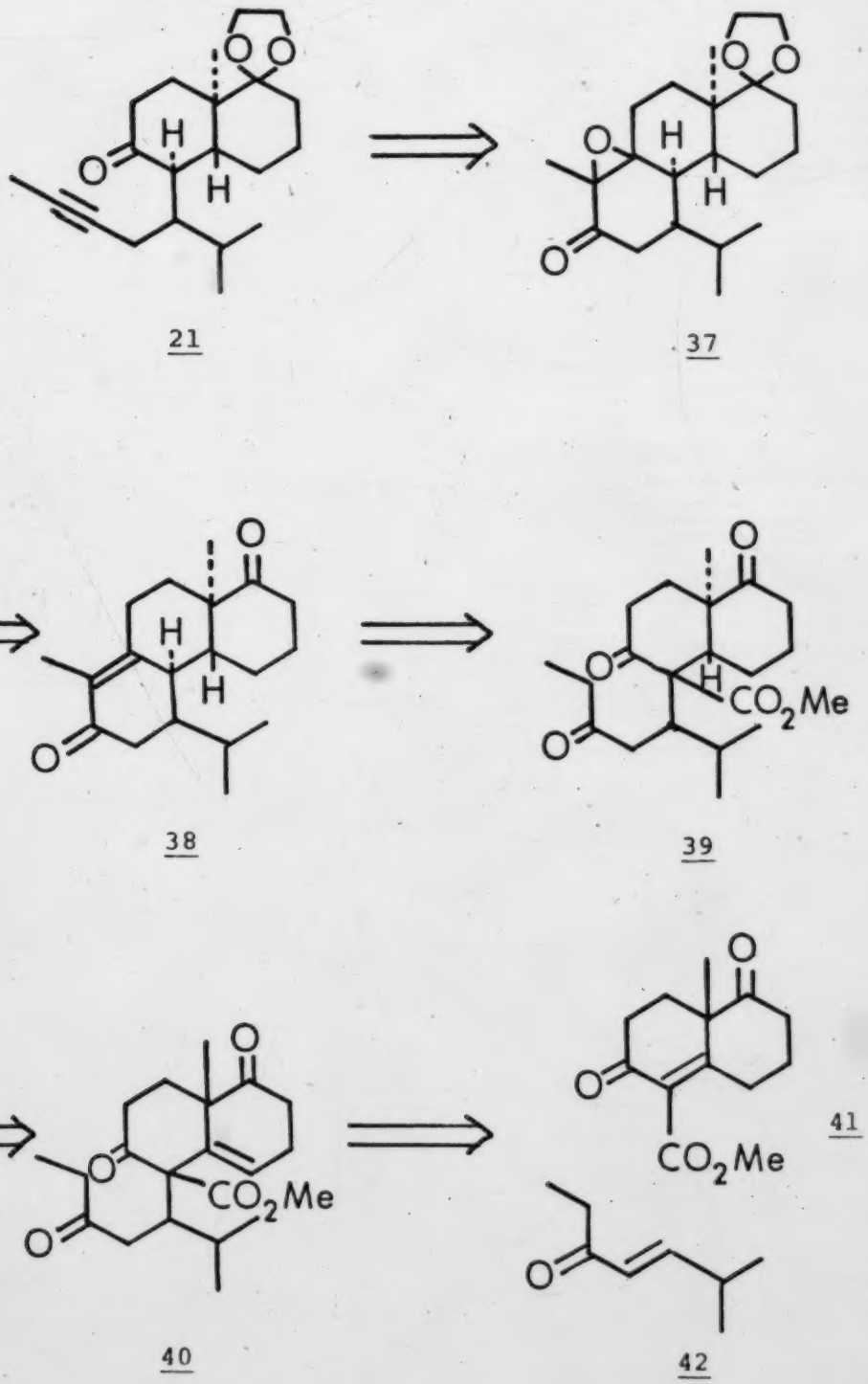
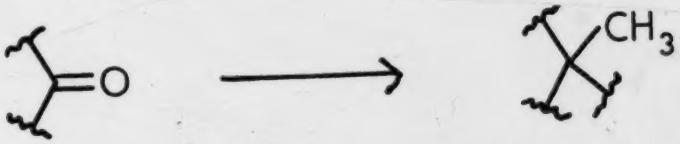
* For an example of this type of transformation see R.E. Ireland et. al., J. Am. Chem. Soc., 96, 3333 (1974).

Scheme 4. Alternate synthesis of 21



21 37 38 39 40 41 42

following transformation is encountered.



This reductive geminal alkylation is a difficult transformation and it must be carried out stereoselectively. Although the acetylene-tertiary alcohol cyclization solves this problem admirably, other direct methods are lacking. Since we were unable to prepare a suitable precursor for this reaction the Robinson annulation approach to the synthesis of cyathins was abandoned.

Experimental

Mass spectra were recorded on an A.E.I. MS-50 mass spectrometer and are reported as m/e (relative intensity). Unless diagnostically significant only peaks at least 20% as intense as the base peak are reported. Infrared spectra were recorded on a Perkin-Elmer Model 421 dual grating spectrophotometer. Proton magnetic resonance (^{1}HMR) spectra were measured on a Varian HA-100 spectrometer with TMS as the internal standard. Carbon magnetic resonance (^{13}CMR) spectra were measured on a Bruker WP-60 with TMS as the internal standard.

Preparative gas-liquid chromatography (PGLC) was performed on a 5' x 1/4" column packed with 5% carbowax on chromosorb W 80-100 mesh at 180°C. Silica gel (Woelm, < 0.063 mm) was used for column chromatography. Preparative thick layer chromatography (PTLC) was carried out on 1.0 mm layers of silica gel G (E. Merck, Darmstadt) containing 1% electronic phosphor (General Electric, Cleveland) and materials were detected by uv (254 mm) or by spraying with 30% H_2SO_4 and charring.

Skellysolve B refers to Skelly Oil Company light petroleum b.p. 62-70°.

2,2-Dimethylcycloheptanone (4).

The β-ketoester 3[30] (3.0 gm) was added to 15% H_2SO_4 (50 ml) and was refluxed under nitrogen for 30 hr

and the resulting mixture was extracted with $CHCl_3$. The organic layers were combined, washed with 2.5 N NaOH, water, dried ($MgSO_4$), and the solvent evaporated to give a yellow liquid which was distilled (69-73°/12 Torr) to give 4 as a colorless liquid (1.75 gm, 85%).
IR (neat): 1705 cm^{-1}.
^{1}HMR ($CDCl_3$) δ: 2.50 (m, 2 H, C-7 H's), 1.61 (m, 8 H, C-3-6 H's), 1.08 (s, 6 H, C-2 CH_3's).
MS: m/e calcd. for $C_9H_{16}O$: 140.1201; found: 140.1204 (35), 107 (21), 98 (24), 97 (22), 96 (31), 69 (100), 56 (75), 55 (59).

7,7-Dimethylcyclohept-2-enone (5).

To dry THF (35 ml) under nitrogen at -78° was added diisopropylamine (1.50 ml, 10.7 mmol) followed by 1.6 N n-butyllithium (6.5 ml, 10.4 mmol). After stirring for 30 min, 4 (1.19 gm, 8.5 mmol) in THF (5 ml) was added dropwise. This solution was stirred for 15 min and phenylselenium chloride (1.91 gm, 10 mmol) in THF (15 ml) was added rapidly. The resulting cold solution was poured onto 0.5 N HCl (75 ml) and 50% ether-pentane (50 ml). The organic layer was separated, washed with water, sat. $NaHCO_3$, brine, dried ($MgSO_4$), and the solvent evaporated to give the crude α-phenylselenide.

The crude selenide was dissolved in CH_2Cl_2 (15 ml) and cooled in a dry ice-acetone bath. Ozone was bubbled

in until a blue color persisted. The excess O_3 was removed with nitrogen, diisopropylamine (1.5 ml) was added and the cold solution poured onto refluxing CCl_4 (50 ml). The resulting solution was allowed to cool to 25°, washed with 1 N HCl, sat. $NaHCO_3$, dried ($MgSO_4$), and the solvent evaporated to give a yellow liquid. Column chromatography ($CHCl_3$) gave a slightly colored liquid (0.91 gm) which was a mixture consisting of ~80% (GC) of the desired compound 5 (~65% yield). A pure sample obtained by PGLC had the following spectral properties:

IR (neat): 1660 cm^{-1}.

^{1}HMR ($CDCl_3$ δ: 6.26 (dt, J = 12, 4 Hz, 1 H, C-3 H), 5.90 (dt, J = 12, 2 Hz, 1 H, C-2 H), 2.37 (m, 2 H, C-4 H's), 1.70 (m, 4 H, C-5,6 H's), 1.14 (s, 6 H, C-7 CH_3's).

MS: m/e calcd. for $C_9H_{14}O$: 138.1049; found: 138.1047 (69), 110 (36), 95 (67), 95 (20), 82 (58), 82 (33), 81 (34), 81 (73), 70 (100), 69 (70), 68 (89), 67 (55).

11,11-Dimethyl-1,4-dioxaspiro[4.6]undec-7-ene (6).

A mixture of the crude enone 5 (900 mg), ethylene glycol (1.5 ml) and p-toluenesulfonic acid (~20 mg) in benzene (25 ml) was heated under reflux overnight with removal of water by a Dean-Stark trap. The solution was washed with water, sat. $NaHCO_3$, brine, dried ($MgSO_4$) and the solvent evaporated to give a yellow liquid

(1.145 gm) which was a mixture of several compounds consisting of ~50-60% (GC) of the desired 6. A pure sample obtained by PGLC had the following spectral properties:

IR (neat): 3020, 1375, 1355, 1110 cm^{-1}.

^{1}HMR ($CDCl_3$) δ:* 5.83 (dt, J = 11, 5.5 Hz, 1 H, C-8 H), 5.50 (dt, J = 11, 5.5 Hz, 1 H, C-7 H), 3.90 (s, 4 H, C-2,3 H's), 2.37 (dd, J = 5.5, 1 Hz, 2 H, C-6 H's), 2.15 (m, 2 H, C-9 H's), 1.50 (m, 2 H, C-10 H's), 1.01 (s, 6 H, C-11 CH_3's).

MS: m/e calcd. for $C_{11}H_{18}O_2$: 182.1315; found: 182.1311 (29), 167 (31), 127 (24), 126 (100), 125 (87), 113 (71), 99 (57), 86 (21).

cis-11,11-Dimethyl-7,8-dihydroxy-1,4-dioxaspiro[4.6]-undecane (7).

The crude acetal 6 (1.01 gm) was dissolved in THF (20 ml) containing pyridine (1.0 ml). The solution was cooled to -70° and osmium tetroxide (1 gm) in THF (5 ml) was added dropwise. The solution was allowed to warm to 25° and was stirred for 2 hr. The osmate ester was decomposed with H_2S and the mixture was filtered, washed with ether and the solvents evaporated to give the crude diol 7. Column chromatography ($CHCl_3$:MeOH, 9:1) afforded 7 (402 mg, ~32% overall yield from 4).

* Assignments were confirmed by decoupling experiments.

IR ($CHCl_3$): 3660, 3420 (br) cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 3.93 (m, 8 H), 2.2-1.2 (m, 8 H), 1.05 (s, 3 H) and 0.86 (s, 3 H) (C-11 CH_3's).

MS: m/e calcd. for $C_{11}H_{20}O_4$: 216.1361; found: 216.1359 (1), 115 (100).

1-Methoxy-2,2-dimethyl-6-exohydroxy-8-oxabicyclo[3.2.1]-octane (8).

The diol acetal 7 (300 mg) was dissolved in methanol (15 ml) and a few drops of sat. HCl/methanol were added. The solution was stirred at 25° for 24 hr, poured onto sat. $NaHCO_3$ (30 ml), extracted with $CHCl_3$, dried ($MgSO_4$) and the solvent evaporated to give 8 (217 mg, 85%).

IR ($CHCl_3$): 3590, 3420 (br) cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 4.13 (m, 2 H, C-5,6 H's), 3.34 (s, 3 H), OCH_3), 2.27 (dd, J = 15, 7 Hz, 1 H, C-7 endo H), 1.75 (dd, J = 15, 1.5 Hz, 1 H, C-7 exo H), 1.05 (s, 3 H) and 0.86 (s, 3 H) (C-2 CH_3's).

MS: m/e calcd. for $C_{10}H_{18}O_3$: 186.1255; found: 186.1255 (18), 168 (18), 131 (19), 128 (32), 113 (96), 108 (41), 94 (22), 70 (23), 56 (100).

1-Methoxy-2,2-dimethyl-8-oxabicyclo[3.2.1]octane-6-one (9).

The alcohol 8 (150 mg) was dissolved in acetone (6 ml) and Jones' reagent was added dropwise until the orange color persisted. Excess reagent was destroyed

with 2-propanol. Solid $NaHCO_3$ was added and after filtration the solvent was evaporated to give the ketone 9 (119 mg, 80%).

IR (neat): 1760 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 4.22 (m, 1 H, C-5 H), 3.36 (s, 3 H, OCH_3), 2.66 (d, J = 18 Hz), and 2.32 (d, J = 18 Hz) (C-7 H's), 1.15 (s, 3 H), and 0.92 (s, 3 H) (C-2 CH_3's).

MS: m/e calcd. for $C_{10}H_{16}O_3$: 184.1099; found: 184.1097 (34), 129 (56), 114 (27), 110 (21), 97 (49), 65 (34), 56 (100), 55 (24), 55 (44).

1-Methoxy-2,2-dimethyl-8-oxabicyclo[3.2.1]octane-6-spirooxirane (10).

To dry dimethyl sulfoxide (DMSO) (3 ml) was added NaH (50% dispersion, 28 mg) and the mixtured was stirred under nitrogen at 75° for 30 min after which time the solid had dissolved. The solution was allowed to cool to 25°, THF (5 ml) was added and the solution cooled to 0°. Trimethyl sulfonium iodide (114 mg) in DMSO (2 ml) was added dropwise over 3 min. The ketone 9 in THF (2 ml) was added dropwise over 3 min and the resulting solution stirred at 0° for 15 min and at 25° for 1 hr. The solution was diluted with water (50 ml), extracted with $CHCl_3$, the organic layers combined, dried ($MgSO_4$) and the solvent evaporated to give after PTLC (Skellysolve B:acetone, 3:1) the epoxide 10 as an oil (64 mg, 66%).

IR (neat): 1380, 1360, 1300, 1275, 1200, 1150, 1130, 1080, 1060, 1040, 985 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 3.97 (m, 1 H, C-5 H), 3.32 (s, 3 H, OCH_3), 2.95 (s, 2 H, C-3' H's), 2.35 (d, J = 15 Hz, 1 H), and 1.93 (d, J = 15 Hz, 1 H) (C-7 H's), 1.10 (s, 3 H), and 0.94 (s, 3 H) (C-2 CH_3's).

(5S)-2-Methyl-2,3-epoxy-5-(1-methyethenyl)cyclohexanone (25).

To a solution of (+)-carvone (24) (100 gm) and 30% H_2O_2 (250 ml) in methanol (1 ℓ) was added 2.5 N NaOH (80 ml) dropwise maintaining the temperature at 10-20°. The solution was stirred at 25° for 2 hr, diluted with water (2 ℓ) and extracted with ether. The organic layers were combined, washed with sat. $NaHCO_3$, brine, dried ($MgSO_4$) and the solvent evaporated to give the epoxide 25 (100 gm, 90%).

$[\alpha]_D^{25}$ + 76° (c 0.41, $CHCl_3$).

IR (neat): 1715, 1660 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 4.74 (m, 2 H, C-2' H's), 3.44 (m, 1 H, C-3 H), 1.72 (s, 3 H, C-1' CH_3), 1.41 (s, 3 H, C-2 CH_3).

^{13}CMR ($CDCl_3$) δ: 205.5 (s, C-1), 146.6 (s, C-1'), 110.6 (s, C-2'), 61.4 (d, C-3), 58.9 (s, C-2), 41.9 (t, C-6), 35.2 (d, C-5), 28.9 (t, C-4), 20.6 (q, C-1' CH_3), 15.3 (q, C-2 CH_3).

MS: m/e calcd. for $C_{10}H_{14}O_2$: 166.0995; found: 166.0995

(3), 138 (22), 123 (40), 109 (25), 95 (45), 85 (70), 81 (32), 68 (30), 67 (40), 55 (25), 53 (21).

ANALYSIS: calcd. for $C_{10}H_{14}O_2$: C 72.76, H 8.48; found: C 72.80, H 8.46.

(5S)-2-Methyl-2,3-epoxy-5-(1-methylethyl)cyclohexanone (26).

The ketone 25 was dissolved in ether (200 ml) and hydrogenated on a Paar apparatus at 50 psi in the presence of PtO_2 (0.75 gm) until one equivalent of H_2 was absorbed. Filtration and evaporation of the solvent gave 26 (47 gm, 93%).

$[\alpha]_D^{25}$ + 94° (c 0.51, $CHCl_3$).

IR (neat): 1715 cm^{-1}

^{1}HMR ($CDCl_3$) δ: 3.40 (d, J = 3.5, 1 H, C-3 H), 1.41 (s, 3 H, C-2 CH_3), 0.90 (d, J = 6.5 Hz, 3 H), and 0.87 (d, J = 6.5 Hz, 3 H) (C-1' CH_3's).

^{13}CMR ($CDCl_3$) δ: 206.7 (s, C-1), 61.5 (d, C-3), 58.9 (s, C-2), 40.7 (t, C-6), 34.0 (d, C-5), 31.8 (d, C-1'), 27.3 (t, C-4), 19.3 (q), and 19.6 (q) (C-1' CH_3's).

MS: m/e calcd. for $C_{10}H_{16}O_2$: 168.1150; found: 168.1149 (27), 97 (86), 83 (28), 71 (28), 69 (20), 55 (38), 43 (100).

ANALYSIS: calcd. for $C_{10}H_{16}O_2$: C 71.39, H 9.58; found: C 71.33, H 9.59.

(3R)-3-(1-Methylethyl)hept-5-ynal (28).

The epoxyketone 26 (16.71 gm) was dissolved in benzene (150 ml), the aziridine 41[40] (15.3 gm) added, and the resulting solution stirred at 25°. The reaction was monitored (~ every 8 hr) by evaporation of the solvent (removal of water) and observing the carbonyl band at 1715 cm^{-1} in the infrared spectrum. After 36 hr the infrared spectrum indicated the absence of a carbonyl (1715 cm^{-1}). The resulting crude hydrazone 27 was pyrolized by adding it dropwise to dibutyl phthalate at 175°/12 Torr with concomitant distillation of the products (styrene and 28). The products were fractionally distilled to give 28 (93-96°/12 Torr) (10.64 gm, 70%).

$[\alpha]_D^{25}$ - 19° (c 0.65, $CHCl_3$).

IR (neat): 1720 cm^{-1}

^{1}HMR ($CDCl_3$) δ: 9.82 (t, J = 2 Hz, 1 H, C-1 H), 2.45 (dq, J = 5, 2.5 Hz, C-4 H's), 2.15 (m, 3 H, C-2,3 H's), 1.76 (t, J = 2.5 Hz, 3 H, C-7 H's), 0.90 (d, J = 7 Hz, 3 H), and 0.88 (d, J = 7 Hz, 3 H) (C-1' CH_3's).

^{13}CMR ($CDCl_3$) δ: 202.5 (s, C-1), 77.7 (s) and 77.3 (s) (C-6,7), 45.6 (t, C-2), 39.1 (d, C-3), 30.4 (d, C-1'), 21.4 (t, C-4), 19.2 (q), and 19.3 (q) (C-1' CH_3's), 3.4 (q, C-7).

MS: m/e calcd. for $C_{10}H_{16}O$: 152.1201; found: 152.1197 (7), 109 (24), 109 (26), 108 (74), 97 (33), 93 (100),

91 (30), 82 (26), 81 (40), 79 (33), 77 (37), 69 (56), 67 (36), 55 (66), 53 (49).

(3R,5R) and (3S,5R)-5-(1-Methylethyl)non-1-ene-7-yne-3-ol (29).

The aldehyde 28 in ether (15 ml) was added dropwise over 20 min to a solution of 2.1 N vinyllithium (35.5 ml) in ether (50 ml) under nitrogen maintaining the temperature at -60 to -70°. The solution was allowed to warm to 25° and after stirring for 1 hr, was hydrolyzed with sat. $NaHCO_3$ (150 ml). The organic layer was separated, dried ($MgSO_4$) and the solvent evaporated to give the crude alcohol (22.65 gm). A filtration through alumina (500 gm) eluting first with Skellysolve B then with ether gave after evaporation of the ether fraction the alcohol 29 as a slightly yellow oil (9.38 gm, 73%). This was a ~1:1 mixture of diastereomers by ^{13}Cmr.

IR ($CHCl_3$): 3590, 3460 (br) cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 5.86 (m, 1 H, C-2 H), 5.20 (m, 1 H, C-1 Z H), 5.02 (m, 1 H, C-1 E H), 4.18 (m, 1 H, C-3 H), 2.15 (m, 2 H, C-6 H's), 1.76 (t, J = 2.5 Hz, 3 H, C-9 H's), 1.52 (m, 3 H, C-4,5 H's), 0.90 (d, J = 7 Hz, 3 H), and 0.88 (d, J = 7 Hz, 3 H) (C-1' CH_3's).

^{13}CMR ($CDCl_3$) δ: 142.1, 141.7 (d, C-2), 115.0, 114.1 (t, C-1), 78.5, 76.6 (s, C-7,8), 72.4, 71.1 (d, C-3),

40.4, 39.7 (d, C-5), 38.3 (t, C-4), 30.5, 30.2 (d, C-1'), 21.1, 20.6 (t, C-6), 19.7, 19.4, 19.1 (q, C-1' CH_3's), 3.4 (q, C-9).

MS: m/e calcd. for $C_{11}H_{17}O$ (M^+-CH_3): 165.1279; found: 165.1278 (13), 147 (11), 137 (12), 119 (70), 110 (23), 109 (46), 108 (91), 95 (47), 93 (100), 91 (42), 81 (49), 77 (29).

ANALYSIS: calcd. for $C_{12}H_{20}O$: C 79.94, H 11.18; found: C 79.84, H 11.28.

(5R)-5-(1-Methylethyl)non-1-ene-7-yne-3-one (16).

Jones' reagent (~12 ml) was added dropwise to the alcohol 29 (8.01 gm) in acetone (150 ml) at 10° until the orange color persisted. Excess reagent was destroyed with 2-propanol. The mixture was filtered, poured onto sat. $NaHCO_3$ (250 ml) and extracted with $CHCl_3$. Evaporation of the solvent gave 16 as a slightly yellow oil (7.0 gm, 87%).

IR (neat): 1675, 1610 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 6.30 (m, 2 H, C-2 H and C-1 Z H), 5.76 (dd, J = 9, 3 Hz, 1 H, C-1 E H), 2.59 (m, 2 H, C-4 H's), 2.10 (m, 3 H, C-5,6 H's), 1.73 (t, J = 2.5 Hz, 3 H, C-9 H's), 0.89 (d, J = 7 Hz, 6 H, C-1' CH_3's).

^{13}CMR ($CDCl_3$) δ: 200.5 (s, C-3), 137.1 (d, C-2), 127.5 (t, C-1), 77.5 (s), and 77.1 (s) (C-7,8), 41.1 (t, C-4), 39.8 (d, C-5), 30.4 (d, C-1'), 20.9 (t, C-6), 19.34 (q,

C-1' CH_3's), 3.4 (q, C-9).

MS: m/e calcd. for $C_{12}H_{18}O$: 178.1371; found: 178.1364 (2), 163 (9), 135 (28), 123 (18), 108 (30), 93 (100), 91 (22), 77 (21), 55 (90).

ANALYSIS: calcd. for $C_{12}H_{18}O$: C 80.83, H 10.18; found: C 80.32, H 10.06.

2-Methyl-2-((5R)-5-isopropylnon-7-yne-3-one)-1,3-cyclohexanedione (18).

The dione 17 (4.80 gm) was suspended in dry 1,2-dimethoxyethane (DME) (200 ml) and NaH (35 mg) was added. After stirring for 15 min the enone 16 (6.19 gm) in DME (50 ml) was added dropwise over 30 min. The solution was heated under reflux for 40 min. After cooling to 25°, water (150 ml) was added and the solution extracted with CH_2Cl_2. The organic layers were combined and washed with ice-cold 5% NaOH, water, dried ($MgSO_4$) and the solvent evaporated to give the Michael adduct 18 as a viscous oil (9.17 gm, 87%).

IR (neat): 1710 (sh), 1690 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 1.75 (t, J = 2.5 Hz, 3 H, C-9' H's), 1.25 (s, 3 H, C-2 CH_3), 0.86 (d, J = 6 Hz), and 0.84 (d, J = 6 Hz) (isopropyl CH_3's).

^{13}CMR ($CDCl_3$) δ: 209.9 (s, C-1,3), 209.4 (s, C-3'), 77.4 (s, C-7',8'), 64.4 (s, C-2), 44.1 (t, C-4'), 39.2 (d, C-5'), 38.0 (t, C-2'), 37.8 (t, C-4,6), 30.0 (t,

C-5), 30.0 (d, isopropyl CH), 20.9 (t, C-6'), 19.6 (q, isopropyl CH_3's), 19.3 (q, C-2 CH_3), 17.7 (t, C-1'), 3.4 (q, C-9').

MS: m/e calcd. for $C_{19}H_{28}O_3$: 304.2038; found: 304.2049 (3), 261 (19), 181 (40), 179 (21), 139 (68), 135 (23), 127 (100), 126 (41), 111 (42), 93 (45), 55 (25).

2-Methyl-2-((5R)-5-isopropylnon-7-yne-3-one)cyclohexanone-3-spiro-2'-1,3-dioxolan (35).

A solution of 18 (3.15 gm), and 2-methyl-2-ethyl-1,3-dioxolan (2 ml) in dry benzene (150 ml) was acidified with dry HCl to pH < 1. An additional 2 ml of the dioxolan was added after 2 days and, following a further 2 day reaction period, the mixture was washed with sat. $NaHCO_3$, dried ($MgSO_4$) and the solvent evaporated to give the acetal 35 (3.12 gm, 85%).

IR (neat): 1705 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 3.94 (s, 4 H, dioxolan H's), 1.75 (t, J = 2.5 Hz, 3 H, C-9' H's), 1.03 (s, 3 H, C-2 CH_3), 0.85 (brd, J = 7 Hz, 6 H, isopropyl CH_3's).

MS: m/e calcd. for $C_{21}H_{32}O_4$: 348.2300; found: 348.2301 (18), 183 (43), 113 (17), 99 (100), 55 (21).

CHAPTER IV

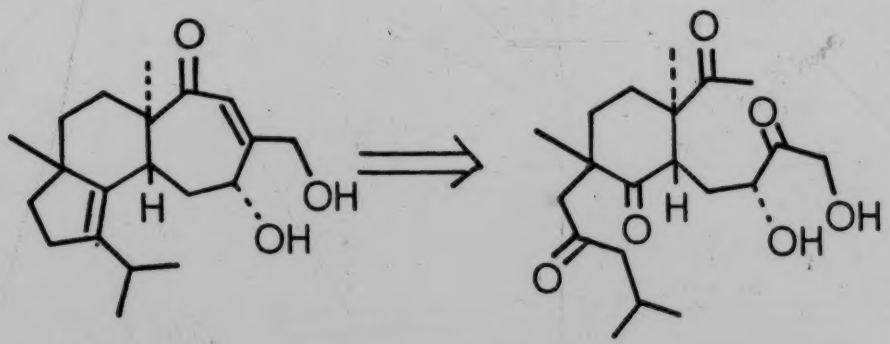
A DIELS-ALDER APPROACH TO THE SYNTHESIS OF CYATHINS

> Often in the course of synthetic work one or two key ideas set the style, development, and outcome of the investigation, while providing the flexibility essential for any long journey through unknown territory, beset with perils which at best can be only dimly foreseen.[48]

Discussion

Because of the failure of the Robinson annulation approach to the synthesis of cyathins outlined in the previous chapter, as well as other somewhat similar approaches[28] involving this type of annulation, we sought a new strategy for the construction of the cyathin diterpenoids.

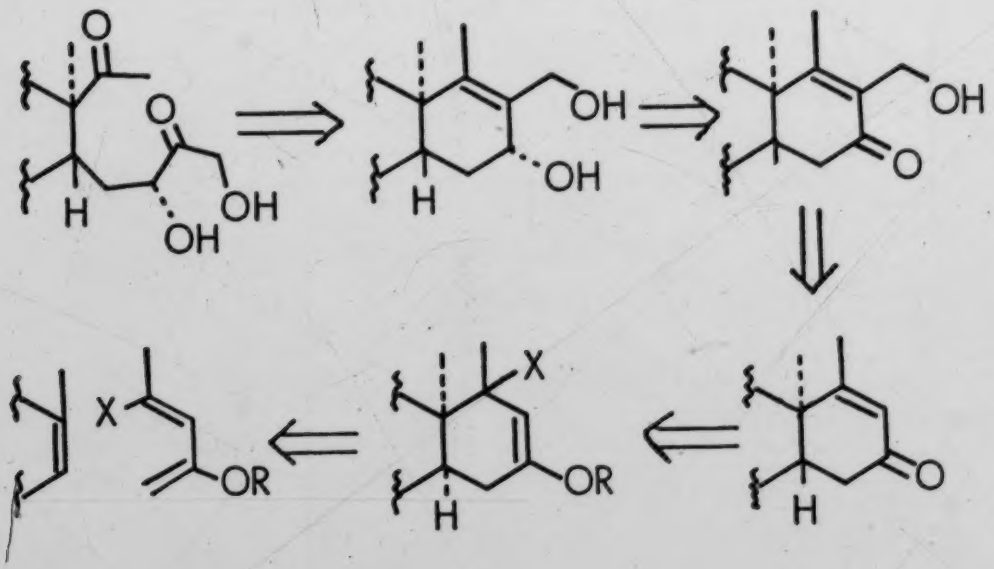
Analysis of the structure of cyathin A_3 (1) from a retro-synthetic point of view leads to two obvious disconnections. Thus the A and C rings of 1 are seen to



be derivable *via* aldol cyclizations of 1,4 and 1,6 diketones respectively.

The 1,6 diketone comprising the seco C ring can

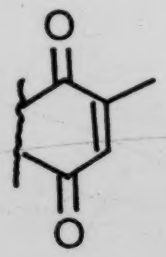
arise by oxidation of an appropriately substituted cyclohexene (see Scheme 1). Of course such an oxidation



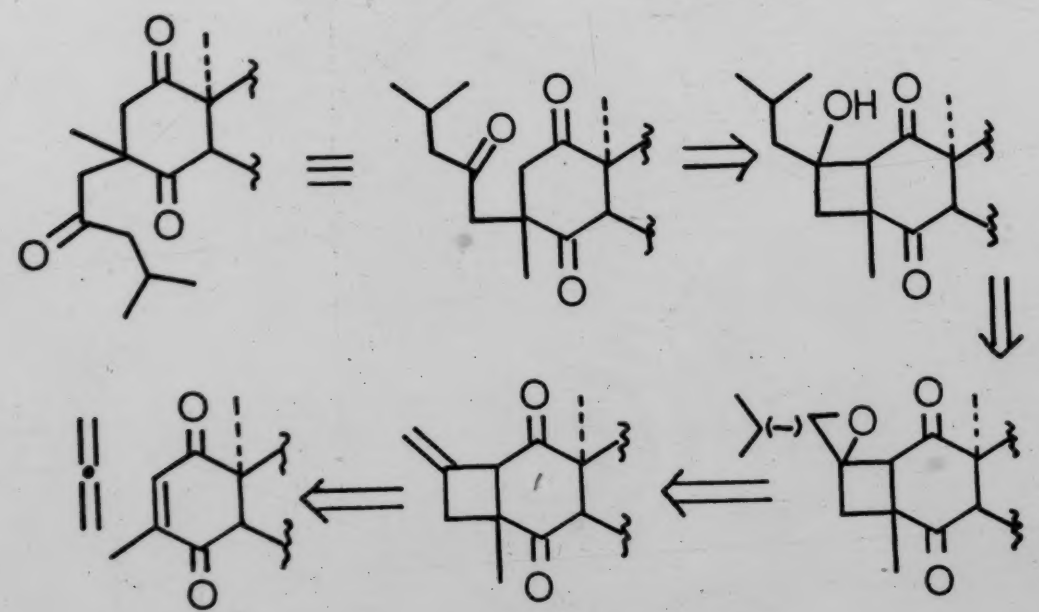
Scheme 1. Retro-synthesis of cyathin C ring

would necessitate the protection of the hydroxyl groups, for example as their acetonide derivative. The required cyclohexene can be obtained from a β-methylcyclohexenone by alkylation of the corresponding dienolate anion with formaldehyde followed by reduction. A Diels-Alder reaction of a 2,4-disubstituted-1,3-pentadiene with an appropriate dienophile should give the desired cyclohexenone after hydrolysis. Since such a Diels-Alder reaction would be expected to give a cis ring junction,

the ring junction hydrogen would require epimerization. This should be easily accommodated by the α-carbonyl from the A ring disconnection. Since 3-substituted enones are poor dienophiles and moreover the carbonyl group controls the regiochemistry of the addition, the required dienophile for such a Diels-Alder reaction is:



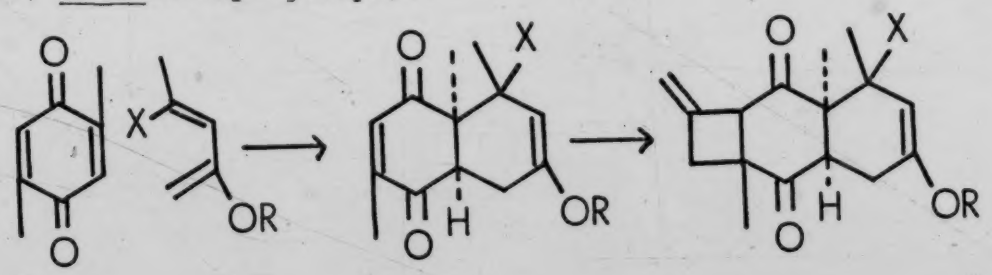
The 1,4 diketone comprising the seco A ring may be seen to arise retro-synthetically from a reverse aldol reaction of a β-hydroxyketone (see Scheme 2). Such a



Scheme 2. Retro-synthesis of cyathin A ring

β-hydroxyketone could be obtained via nucleophilic ring opening of an epoxide derived by oxidation of the photoadduct of allene and an appropriate enedione.

Thus starting with 2,5-dimethyl-p-benzoquinone (2) and performing two electrocyclic reactions (one 4 + 2 and one 2 + 2) should, by the principle of reaction from the least hindered side, produce a tricyclic adduct possessing the desired relative stereochemistry at the ring junctions (i.e., trans methyl groups).



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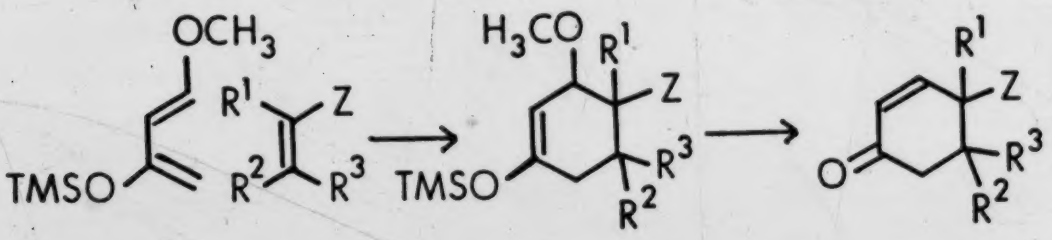
Elaboration of the two newly formed rings to the proper 1,4 and 1,6 diones as outlined in Schemes 1 and 2 should after aldol condensation and removal of the unrequired ketone functions give cyathin A_3 (1).

Results

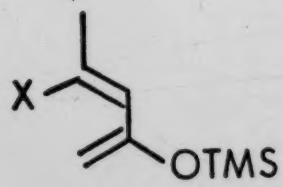
Danishefsky[49] has reported the use of 1,3-dioxygenated-1,3-dienes as reactive dienes in Diels-Alder reactions with activated dienophiles.



Z = $\overset{O}{\overset{\|}{C}}R$, CO_2R, CN TMS = $(H_3C)_3Si-$

These reactions display a high degree of regioselectivity with the electron withdrawing group Z controlling the orientation of the addition as shown.

The diene required for our proposed reaction with the quinone 2 is of generalized structure 3. Inubushi



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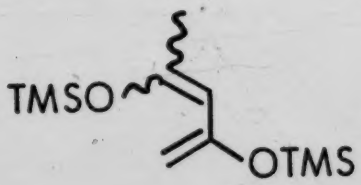
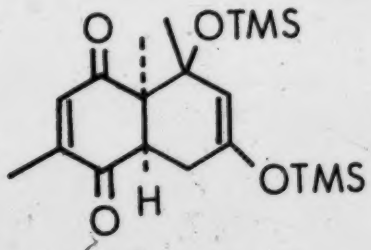


4

et. al[50] have reported the preparation of 2,4-bistrimethylsilyloxy-1,3-pentadiene (4) and its use in Diels-Alder reactions. Thus acetylacetone in triethylamine was treated with chlorotrimethylsilane in the presence of $ZnCl_2$ to give after distillation the diene 4 in 90% yield. ^{1}Hmr revealed the diene to be an ~1:1 mixture of stereoisomers (δ 2.05, s, 3H, and δ 1.85, s, 3H, C-4 CH_3).

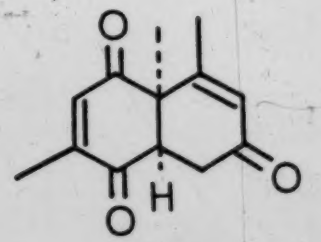
The Diels-Alder reaction of the diene 4 with the quinone 2 was investigated. Whereas heating a solution

of 2 and 4 (2.2 equiv.) under reflux for 3 days in benzene or toluene led to approximately 50 and 75% conversion respectively by thin layer chromatography (tlc), reaction in refluxing xylene led to complete conversion after 40 hr. Evaporation of the volatiles followed by a bulb to bulb distillation gave the adduct 5 in 91% yield. ^{1}H and ^{13}Cmr suggested the



5

adduct to be a single stereoisomer. Although the relative stereochemistry of the tertiary allylic ether in 5 was not determined, it is not crucial to the overall synthetic strategy since at a later stage it will be subjected to elimination. The adduct 5 was further characterized by hydrolysis in methanol with trifluoroacetic acid to the crystalline trione 6.

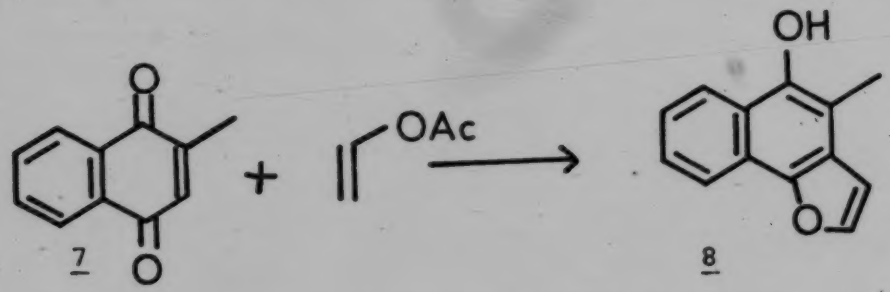


6

In the ^{1}Hmr spectrum of 6 the three non-methyl aliphatic protons appear as an ABX pattern with J_{AB} = 4 Hz,

J_{AX} = 6 Hz, and J_{BX} = 18 Hz confirming the stereo- and regiochemistry of the Diels-Alder addition. The photoaddition of allene to the enedione 5 was next investigated.

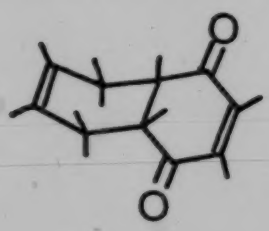
The work of Liu[51] suggests that the 2 + 2 photoaddition of olefins to enediones leads to a product with the regiochemistry that would be expected from a "normal" β-substituted enone. For example the addition



7 8

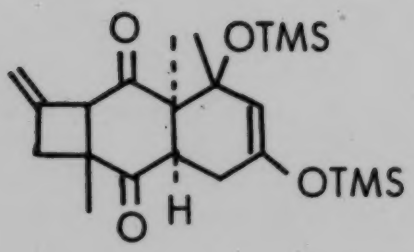
of vinyl acetate to the naphthoquinone 7 gives after basic workup the naphthofuran 8 in good yield. This result is not entirely unexpected since 2-substituted enones are generally poor reactants in this type of photochemical addition. Thus we felt that the addition of allene to 5 would proceed with the desired regiochemistry (see Scheme 2). Weisner has studied the addition of allene and other olefins to enones and has described an addition rule to predict the stereochemistry of addition of these reactions.[52] His rule states that reaction proceeds from a conformationally flexible (at least at the β-carbon) excited state in which the β-substituent of the starting enone assumes its thermo-

dynamically more stable configuration. Such a rule is difficult to apply to a compound such as 5. The X-ray structures of several tetrahydronaphthoquinones such as 5 have been determined[53] and it was found that they all possessed the conformation shown,[54] in which the

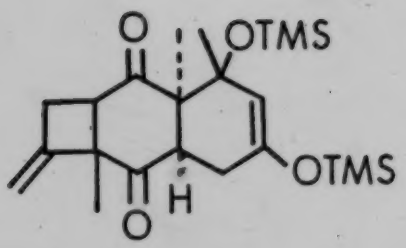


cyclohexene ring exists in a half-chair form cis fused to an almost planar cyclohexenedione ring. In an excited state where the β-carbon of the enedione of 5 (i.e. the carbon bearing methyl) is conformationally flexible it is difficult to say what the more stable conformation would be. This is especially true when the configuration of the allylic ether carbon is not known. However in photodimerization of these types of compounds it has been shown that the product is the one with the sterically least congested cis-anti-cis-anti-cis-anti-cis stereochemistry.[54] With this in mind we were hopeful that the addition of allene to 5 would result in the desired anti stereochemistry (see Scheme 2).

In the event irradiation of a THF solution of 5 and excess allene at -40 to -50° gave after evaporation of the volatiles the crude adducts 9. Hydrolysis of

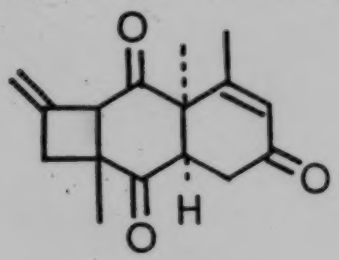


9a

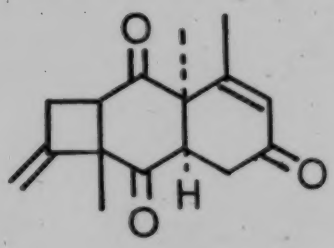


9b

the photoadduct 9 with Rexyn 101 acidic ion exchange resin in 30% methanol/THF gave the crystalline trione 10 in 55 to 65% overall yield from the quinone 2 after chromatography (florisil, ether) and recrystallization (CCl_4-cyclohexane). A 270 MHz ^{1}Hmr spectrum revealed



10a

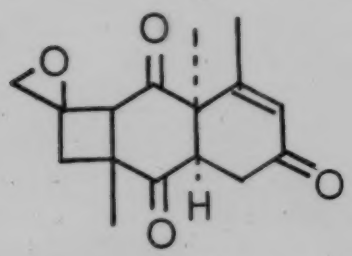


10b

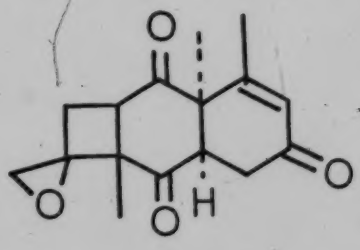
that 10 was an ~4:1 mixture of 10a and 10b. The signals for the exocyclic methylene protons (δ 5.16, dq, J = 1.1, 2.7 Hz, 1H; δ 5.01, ddt, J = 1.1, 3.3, 2.2 Hz, 1H) and the 4,6 ring junction proton (δ 3.70, dq, J = 2.2, 2.7 Hz, 1H) confirmed that the photoaddition had occurred with the desired regiochemistry in the major product 10a. As well, the signal for the other methine proton (δ 3.41, dd, J = 4.5, 3.8 Hz, 1H) supported the presence of a cis 6,6 ring junction in 10a as shown. Although 10a and 10b were co-crystalline (they are completely

homogeneous by tlc and thus could not be separated), comparison of the spectral data (^{1}Hmr and ^{13}Cmr) of the major and minor isomer of 10 led us to speculate that the minor isomer was the regioisomer 10b. This was confirmed by later experiments (vide infra). We were unable to assign the relative stereochemistry of the ring junctions in 10 (i.e., syn or anti) but continued on with the hope that this key point would become clear at a later stage.

The exocyclic double bond of 10 was selectively oxidized with meta-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 to give a crystalline mixture of epoxides 11 in high yield after trituration with ether.

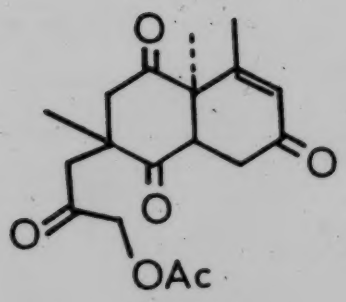


11a

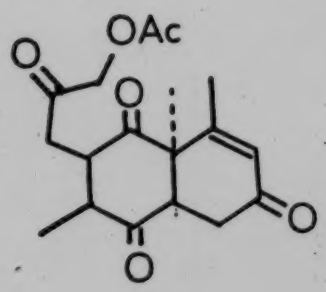


11b

Acid catalyzed hydrolysis of the epoxides 11 with 1 N $HClO_4$ in refluxing THF gave after acetylation (acetic anhydride-pyridine) a mixture of monoacetates. Spectral data (ir, ^{1}Hmr) for the mixture was consistent with structures 12a and 12b with the former predominating (~3:1). Significantly in the ^{1}Hmr spectrum of the mixture the minor isomer showed a three hydrogen doublet at δ 1.10 (J = 6 Hz) confirming our



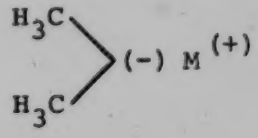
12a



12b

speculation on the regioisomeric nature of the minor products in 9, 10 and 11. The formation of 12 is readily accounted for by hydrolysis of the epoxide function to a diol followed by retro-aldol fragmentation of the resulting β-hydroxyketone.

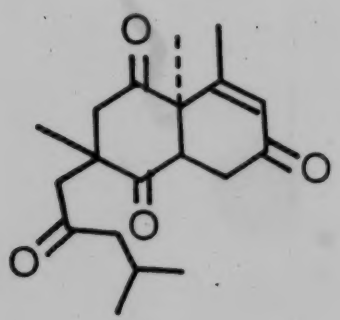
The next stage in the synthetic sequence for elaboration of the cyclobutane in 11 to the A ring of cyathins requires the nucleophilic opening of the epoxide with the generalized nucleophile:



Such a nucleophile must be carefully chosen so as to effect the epoxide opening selectively in the presence of carbonyl functional groups. Lithium dialkylcuprates have been reported to open epoxides in the presence of carbonyls.[55] Although these reagents are also

known[56] to add to enones in a 1,4 fashion we hoped that in our case the enone would be sufficiently sterically hindered to addition to facilitate the selective opening of the epoxide.

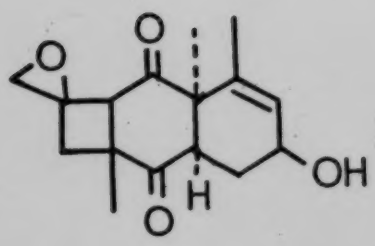
In the event the epoxides 11 were treated with lithium diisopropylcuprate (prepared[57] from isopropyllithium[58] and CuI) in ether for 1 hr at -40°. Workup afforded a complex mixture of products which did not contain detectable amounts of the desired 13.



13

Although the products were not characterized further it appears likely that 1,4 addition to the enone is occurring in competition with epoxide opening.

With the above result in mind it became desirable to first protect the enone system before attempting the epoxide opening. After several unsuccessful attempts to prepare the appropriate N,N-dimethylhydrazone or acetal we focused on the preparation of the allylic alcohol 14.



14

To prepare 14 from 11 a reducing agent was required that would selectively reduce the least sterically hindered carbonyl, selectively reduce enones in a 1,2 fashion, and be inert towards epoxides. Brown[59] has made an extensive study of the reactivity of 9-borabicyclo[3.3.1]nonane (9-BBN) towards various functional groups. On the basis of this study 9-BBN should provide the desired selectivity in the reduction of 11 to 14.

Treatment of 11 with 1.1 equivalents of 9-BBN in THF gave 14 (along with its regioisomer) as its corresponding O-boron adduct as evidenced by the disappearance in the ir spectrum of the enone carbonyl band (1670 cm^{-1}). The crude alcohol 14 could be obtained by treatment of the boron adduct with one equivalent of ethanolamine* in ether and was used directly without further purification.‡ However treatment of 14 or its O-boron adduct

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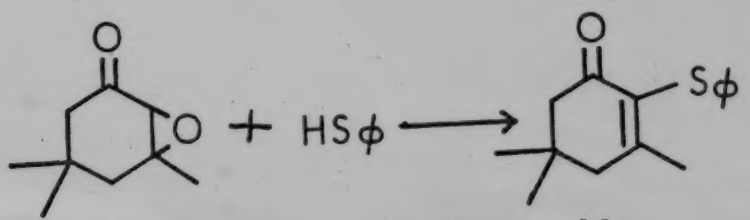
* 9-Alkoxy-9-BBN compounds on treatment with ethanolamine produce the corresponding alcohols and precipitate the 9-BBN moiety as its ethanolamine complex.[60]

‡ The crude 14 was contaminated with substantial quantities of hydrocarbon originating from the 9-BBN reagent used.

with lithium diisopropylcuprate led to complex mixtures of products and this approach was abandoned.

An alternative method for the elaboration of the cyclobutane moiety of 11 into the A ring of cyathins would involve nucleophilic opening of the epoxide with a nucleophile where X = O, S, or N (see Scheme 3). In this way, aldol cyclization of the 1,4-diketone resulting from the epoxide opening would provide a monoprotected (as an enol derivative) 1,2-dione. Removal of the carbonyl followed by hydrolysis of the protecting group would give a cyclopentanone. Condensation with isopropyllithium or isopropylmagnesium bromide and dehydration would then complete the desired transformation.

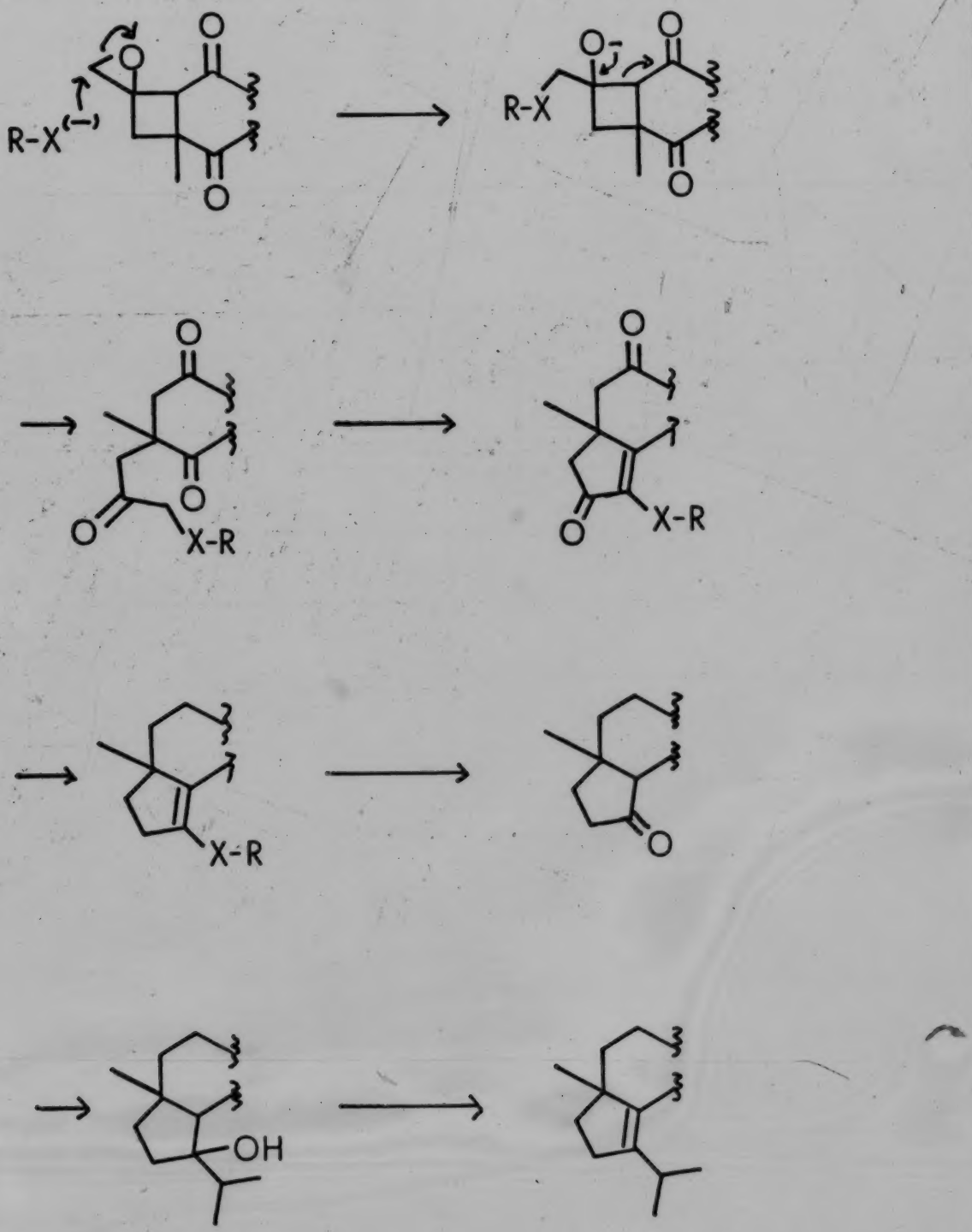
Schultz[61] has described the reaction of epoxyketones with aromatic thiols in the presence of a catalytic amount of base to produce 2-arylthioenones. For example the reaction of isophorone epoxide (15) with benzenethiol in ethanol in the presence of 5 mole % KOH gave 16 in 90% yield. We felt that this reaction might apply



15 16

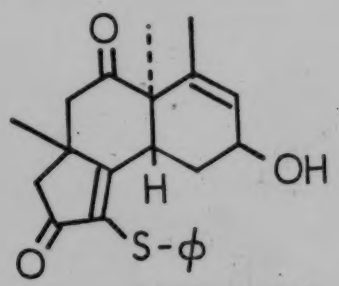
to our proposed (see Scheme 3) transformation. However since thiols are known to efficiently add to enones

Scheme 3. Alternative synthesis of cyathin A ring



in a 1,4 fashion we decided to proceed via the allylic alcohol 14.

Treatment of the crude 14 (prepared as described above) with 1.1 equivalents of benzenethiol in ethanol in the presence of 5 mole % KOH for 8 hr at 0° and 1.5 hr at 75° gave the desired tricyclic dione 17 after



17

workup and trituration with ether.

Examination of the ^{1}Hmr spectrum of 17 suggests that it possesses the desired relative stereochemistry (i.e., trans 6,6 ring junction and trans methyl groups). The signal for the ring junction hydrogen appears at δ 3.62 as a doublet of doublets with J = 11,4 Hz indicative of axial-axial, axial-equatorial couplings. Examination of Drieding models shows that when the methyl groups are cis then the ring junction hydrogen is equatorial (with respect to the cyclohexene ring) and thus the expected couplings would be small (i.e., equatorial-equatorial and equatorial-axial couplings). Moreover if it is assumed that the 9-BBN reduction of the

enone 11 occurs from the convex face of the cis 6,6 ring system then the hydroxyl group is introduced trans to the methyl group at the ring junction. The carbinol hydrogen appears as a broad triplet at δ 4.09 with a J value of ~6 Hz. The coupling constant of the vinyl hydrogen to the carbinol hydrogen is < 2 Hz. Again examination of models shows that if the ring junction is cis then the carbinol hydrogen is pseudo-axial and thus would be expected to have one large and one small coupling to the α-methylene hydrogens. Alternatively if the ring junction is trans then the carbinol hydrogen is pseudo-equatorial and thus would be expected to have two small couplings to the α-methylene hydrogens. The observed signal is a broad triplet which indicates two similar coupling constants. We feel that this result is best explained by a pseudo-equatorial carbinol hydrogen thus indicating a trans ring junction. This point is, however, not wholly unambiguous and the possibility that the ring junction is cis remains.

Conclusion

The tricyclic dione 17 is available in ~30% overall yield in 5 steps from the commercially available 2,5-dimethyl-p-benzoquinone (2) without the need of chromatographic separation. The preparation of 17

shows that the Diels-Alder approach to the synthesis of cyathins is a viable one in that the desired stereochemistry at the ring junctions is obtained stereoselectively. Moreover the functional groups that are present in 17 should be amenable to elaboration to cyathin A_3 along the lines described in Scheme 1 (for the C ring) and Scheme 3 (for the A ring).

The starting point (see Scheme 4) for such a transformation is the removal of the two unrequired ketone functions in 17. Oxidation to the enone followed by alkylation of the corresponding dienolate anion with formaldehyde* should give rise to the α-hydroxymethyl enone. Reduction of the enone should selectively give the desired equatorial alcohol. Protection of the diol (e.g., as the acetonide) and addition of the isopropyl group to the unmasked cyclopentanone would lead to the key intermediate after ozonolysis of the cyclohexene to the 1,6 diketone. An aldol cyclization followed by dehydration would give the known[8] cyathin A_3 acetonide.

Work along these lines is in progress in these laboratories.

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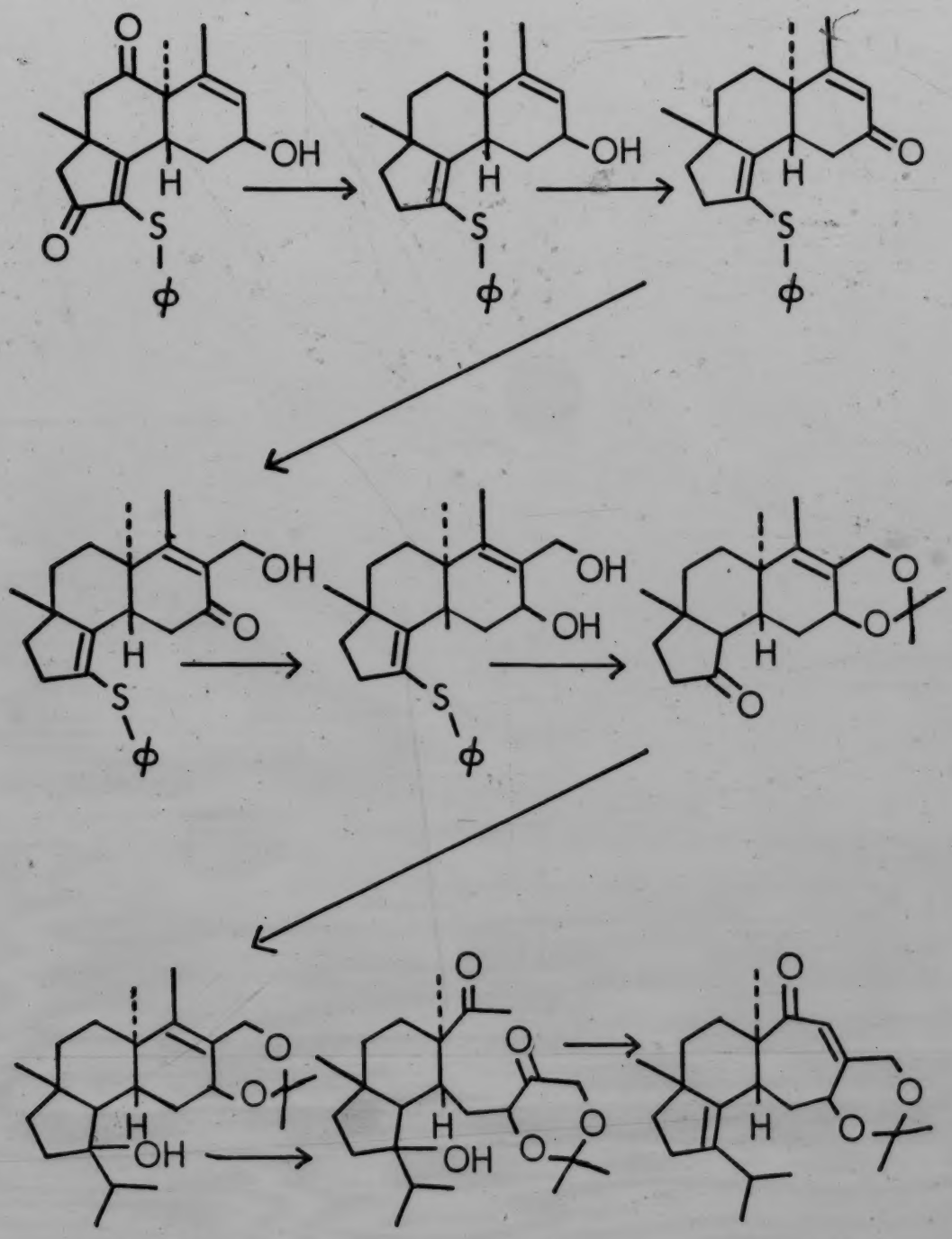
* This alkylation may be easier via the N,N-dimethyl hydrazone derivative.[62]

Scheme 4. Route to cyathin from 17



Experimental

Mass spectra were recorded on an A.E.I. MS-50 mass spectrometer and are reported as m/e (relative intensity). Unless diagnostically significant only peaks at least 20% as intense as the base peak are reported. Infrared spectra were recorded on a Nicolet 7199 FT-IR spectrometer or a Perkin-Elmer Model 297 spectrophotometer. Proton magnetic resonance (^{1}HMR) spectra were recorded on a Varian HA-100 spectrometer with TMS as the internal standard. Carbon magnetic resonance (^{13}CMR) spectra were recorded on a Bruker HFX-90 or WP-60 spectrometer with TMS as the internal standard. Melting points were determined on a Thomas Model 40 micro hot stage apparatus and are uncorrected.

E and Z-2,4-Bistrimethylsilyloxy-1,3-pentadiene (4).

Dry $ZnCl_2$ (3 gm) was added to triethylamine (250 ml) and the mixture was stirred at room temperature until the solid was suspended. Acetylacetone (50 gm) in dry benzene (300 ml) was added followed by dropwise addition over 45 min of chlorotrimethylsilane (190 ml). The mixture was heated to 40° and stirred overnight. Dilution with ether, filtration, concentration under reduced pressure, and distillation (74-76°/3 Torr) afforded the diene 4 (110 gm, 90%) as a colorless liquid. The ^{1}Hmr spectrum of 4 revealed it to be an ~1:1 mixture

of the E and Z isomers.

^{1}HMR ($CDCl_3$) δ: 5.25 (brs, 1H), 4.83 (brs, 1H), 4.70 (brs, 1H), 4.33 (brs, 1H), 4.18 (brs, 1H), 4.10 (brs, 1H), 2.03 (brs, 3H), 1.85 (brs, 3H), 0.22 (brs, 36H).

cis-3,6,7-Trimethyl-7,9-bistrimethylsilyloxybicyclo[4.4.0]-deca-3,8-diene-2,5-dione (5).

A solution of 2,5-dimethyl-p-benzoquinone (2) (10 gm) and the diene 4 (40 gm) in xylene (300 ml) was heated under reflux for 40 hr. The volatiles were removed by evaporation under high vacuum at 70°. Bulb to bulb distillation (125°/0.025 Torr) provided the Diels-Alder adduct 5 as a viscous orange oil (25.5 gm). ^{1}Hmr and ^{13}Cmr suggested the adduct to be a single stereoisomer.

IR (neat): 1684, 1628 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 6.40 (q, J = 1.3 Hz, 1H, C-4 H), 4.94 (t, J = 1.3 Hz, 1H, C-8 H), 3.28 (dd, J = 7.3, 6.7 Hz, 1H, C-1 H), 2.22 (m, 2H, C-9 H's), 1.95 (d, J = 1.3 Hz, 3H, C-3 CH_3), 1.45 (s, 3H) and 1.32 (s, 3H) (C-6,7 CH_3's), 0.16 (s, 9H) and 0.06 (s, 9H) (silyl CH_3's).

^{13}CMR ($CDCl_3$) δ: 200.4 (s) and 200.2 (s) (C-2,5), 149.5 (s, C-3), 146.6 (s, C-9), 137.2 (s, C-4), 112.5 (d, C-8), 74.5 (s, C-7), 56.0 (s, C-6), 51.1 (d, C-1), 29.8 (t, C-10), 27.6 (q, C-7 CH_3), 20.1 (q, C-6 CH_3), 15.5 (q, C-3 CH_3), 2.2 (q) and 0.3 (q) (silyl CH_3's).

MS: m/e calcd. for $C_{19}H_{32}O_4Si_2$: 380.1839; found:

380.1834 (2), 244 (55), 230 (21), 229 (100), 73 (31).

cis-3,6,7-Trimethylbicyclo[3.3.0]deca-3,7-diene-2,5,9-trione (6).

The Diels-Alder adduct 5 (480 mg) was dissolved in methanol (10 ml) and trifluoroacetic acid (~10 mg) was added. The solution was stirred at room temperature for 3 hr, diluted with 10% $NaHCO_3$ (20 ml), extracted with $CHCl_3$, dried (Na_2SO_4), and the solvent evaporated to give the crude 6. Recrystallization from CCl_4 gave 6 (154 mg, 70%) (mp 109-11).

IR (neat): 1680, 1621 cm^{-1}.

^{1}HMR ($CDCl_3$) δ: 6.65 (q, J = 1.5 Hz, 1H, C-4 H), 5.84 (q, J = 1.5 Hz, 1H, C-8 H), 3.17 (m, 2H) and 2.58 (dd, J = 18.6 Hz, 1H) (ABX, J_{AB} = 4 Hz, J_{AX} = 6 Hz, J_{BX} = 18 Hz, C-1,10 H's), 2.01 (d, J = 1.5 Hz, 3H, C-3 CH_3), 1.81 (d, J = 1.5 Hz, 3H, C-7 CH_3), 1.56 (s, 3H, C-6 CH_3).

^{13}CMR ($CDCl_3$) δ: 198.6 (s) and 197.3 (s) (C-2,5), 194.4 (s, C-9), 159.8 (s, C-7), 150.3 (s, C-3), 136.3 (d, C-4), 127.9 (d, C-8), 54.3 (s, C-6), 53.3 (d, C-1), 34.3 (t, C-10), 21.2 (q, C-6,7 CH_3's), 16.1 (q, C-3 CH_3).

MS: m/e calcd. for $C_{13}H_{14}O_3$: 218.0942; found: 218.0938 (100), 176 (40), 123 (17), 96 (77), 68 (82).

ANALYSIS: calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found: C 70.92, H 6.38.

3,8,9-Trimethyl-5-methylene-9,11-bistrimethylsilyl-oxytricyclo[6.4.0.$0^{3,6}$]dodec-10-ene-2,7-dione (9a).

A solution of the adduct 5 (25 gm) and excess allene (250 gm) in dry THF (500 ml) was irradiated through a pyrex filter with a 450 W Hanovia mercury vapor lamp for 20 hr while bubbling nitrogen through the system. The internal temperature was maintained at -40 to -50°. The excess allene was allowed to evaporate followed by evaporation of the solvent at reduced pressure to afford the crude photoadduct 9 as an oil (27 gm). Spectral data (^{1}H and ^{13}Cmr) indicate that 9 is a 4:1 mixture of the 5-methylene (9a) and the 4-methylene (9b) isomers. The ultimate conversion of 9 into 17 indicates that 9a possesses the cis-anti-cis stereochemistry at the ring junctions.

IR (neat): 1708, 1676 cm^{-1}.

^{1}HMR ($CDCl_3$) δ for major isomer 9a: 5.30 (m, 1H) and 5.15 (m, 1H) (C-5 methylene H's), 4.96 (t, J = 1.3 Hz, 1H, C-10 H), 1.63 (s, 3H), 1.52 (s, 3H), and 1.37 (s, 3H) (C-3,8,9 CH_3's), 0.42 (s, 9H) and 0.28 (s, 9H) (silyl CH_3's).

^{13}CMR ($CDCl_3$) δ for major isomer 9a: 211.3 (s) and 206.2 (s) (C-2,7), 148.0 (s, C-11), 140.0 (s, C-5), 112.0 (d, C-10), 110.7 (t, C-5 CH_2), 75.1 (s, C-9), 63.1 (d, C-6), 56.8 (s, C-8), 48.9 (d, C-1), 44.9 (s, C-3), 43.3

(t, C-4), 26.0 (t, C-12), 28.0 (q), 24.4 (q), 21.5 (q) (C-3,8,9 CH_3's), 2.28 (q) and 0.36 (q) (silyl CH_3's). MS: m/e calcd. for $C_{21}H_{33}O_4Si_2$ (M^+-CH_3): 405.1917; found: 405.1916 (18), 244 (55), 230 (22), 229 (100), 149 (27), 147 (16), 73 (59).

3,8,9-Trimethyl-5-methylenetricyclo[6.4.0.$0^{3,6}$]dodec-9-ene-2,7,11-trione 10a.

The photoadduct 9 (27 gm) was dissolved in 30% methanol/THF (150 ml) and Rexyn 101 acidic ion exchange resin (~5 gm) was added. The mixture was stirred at room temperature for 30 hr, poured onto 10% $NaHCO_3$ (300 ml), extracted with $CHCl_3$, washed with sat. $NaHCO_3$, dried (Na_2SO_4), and the solvent evaporated to give the crude trione 10 (17.5 gm) which was used in the next step without further purification. In reactions run on a smaller scale (i.e., starting with 2 gm of the quinone 2) the crude trione (~3.5 gm) was purified by column chromatography (florosil, ether) to give crystalline 10 (2.2-2.6 gm), which was recrystallized from CCl_4-cyclohexane (mp 120-31). Spectral data (^1H and ^{13}Cmr) indicated that 10 was an ~4:1 mixture of the 5-methylene (10a) and 4-methylene (10b) isomers. The ultimate conversion of 10 into 17 indicates that 10a possesses the cis-anti-cis stereochemistry at the ring junctions.

IR (neat): 1701, 1676, 1619 cm^{-1}.

^{1}HMR ($CDCl_3$)* δ for major isomer 10a: 5.83 (q, J = 1.5 Hz, 1H, C-10 H), 5.16 (dq, J = 1.1, 2.7 Hz, 1H) and 5.01 (ddt, J = 1.1, 3.3, 2.2 Hz, 1H) (C-5 methylene CH_2), 3.70 (dq, J = 2.2, 2.7 Hz, 1H, C-6 H), 3.41 (dd, J = 4.5, 3.8 Hz, 1H, C-1 H), 3.08 (dd, J = 18, 3.8 Hz, 1H) and 2.53 (dd, J = 18, 4.5 Hz, 1H) (C-11 H's), 2.86 (m, 2H, C-4 H's), 1.80 (d, J = 1.5 Hz, 3H, C-9 CH_3), 1.53 (s, 3H, C-8 CH_3), 1.37 (s, 3H, C-3 CH_3).

^{13}CMR ($CDCl_3$) δ for major isomer 10a: 209.8 (s) and 204.0 (s) (C-2,7), 157.8 (s, C-9), 139.8 (s, C-5), 128.6 (d, C-10), 110.5 (t, C-5 CH_2), 61.1 (d, C-6), 54.9 (s, C-8), 51.5 (d, C-1), 45.1 (s, C-3), 43.1 (t, C-4), 34.3 (t, C-12), 23.6 (q, C-3,8 CH_3's), 21.0 (q, C-9 CH_3).

MS: m/e calcd. for $C_{16}H_{18}O_3$: 258.1256; found: 258.1247 (4), 216 (40), 177 (37), 172 (27), 171 (33), 157 (25), 149 (24), 123 (45), 122 (24), 109 (22), 108 (24), 94 (26), 80 (86), 79 (100), 77 (34).

ANALYSIS: calcd. for $C_{16}H_{18}O_3$: C 74.40, H 7.02; found: C 74.08, H 7.03.

3,8,9-Trimethyltricyclo[6.4.0.$0^{3,6}$]dodec-9-ene-2,7,11-triene-5-spirooxirane 11a.

The triones 10 (1.75 gm) and MCPBA (85%, 1.75 gm) in CH_2Cl_2 (70 ml) were stirred at room temperature for 36 hr.

* Spectrum obtained at 270 MHz.

The solution was washed with 10% sodium bisulfite, water, sat. $NaHCO_3$, brine, dried (Na_2SO_4), and the solvent evaporated to give the crystalline mixture of epoxides 11 (1.58 gm) after trituration with ether. Alternatively the crude triones 10 could be oxidized as above to give the crystalline epoxides 11 in ~45% overall yield from quinone 2 without chromatography. Spectral data (^{1}Hmr and ^{13}Cmr) indicated that 11 was an ~4:1 mixture of the 5-spirooxirane (11a) and the 4-spirooxirane (11b) isomers. The ultimate conversion of 11 into 17 indicates that 11a possesses the cis-anti-cis stereochemistry at the ring junctions.

IR (neat): 1706, 1674, 1616 cm^{-1}.

^{1}HMR ($CDCl_3$) δ for major isomer 11a: 5.81 (q, J = 1.5 Hz, 1H, C-10 H), 3.73 (dd, J = 4, 3 Hz, 1H) and 3.58 (brs, 1H) (oxirane CH_2), 2.82 (s, 1H, C-6 H), 1.77 (d, J = 1.5 Hz, 3H, C-9 CH_3), 1.55 (s, 3H, C-8 CH_3) 1.41 (s, 3H, C-3 CH_3).

^{13}CMR ($CDCl_3$) δ for major isomer 11a: 208.8 (s) and 204.6 (s) (C-2,7), 195.0 (s, C-11), 157.7 (s, C-9), 129.1 (d, C-10), 63.8 (s, C-5), 54.4 (s, C-8), 53.3 (t, C-5 CH_2), 48.6 (d) and 46.0 (d) (C-1,6), 42.2 (s, C-3), 34.1 (t) and 33.2 (t) (C-4,12), 22.2 (q) and 20.4 (q X2) (C-3,8,9 CH_3's).

MS: m/e calcd. for $C_{16}H_{18}O_4$: 274.1205; found: 274.1212 (17), 259 (14), 246 (13), 232 (39), 191 (20), 188 (22);

187 (22), 173 (21), 158 (20), 152 (27), 124 (28), 123 (49), 96 (32), 96 (28), 94 (54), 93 (24), 91 (35), 82 (51), 79 (100), 77 (59), 68 (37), 66 (38), 65 (32), 55 (26), 54 (24), 53 (44), 51 (21).

Acid Hydrolysis of the Epoxides 11.

A solution of the epoxides 11 (541 mg) in THF (15 ml) and 1 N $HClO_4$ (5 ml) was heated under reflux overnight and poured onto sat. $NaHCO_3$ (20 ml), extracted with $CHCl_3$ and the solvents evaporated to give a highly insoluble amorphous solid after trituration with ether. The solid was dissolved in CH_2Cl_2 (15 ml) and pyridine (1 ml) and acetic anhydride (1 ml) were added. The resulting solution was stirred at room temperature for 2.5 hr and the solvents were evaporated under high vacuum at 50° to give 12 as an oil (487 mg). This was an ~3:1 mixture of 12a and 12b respectively.

IR (neat): 1740, 1710 cm^{-1}.

^{1}HMR ($CDCl_3$) δ for major isomer 12a: 5.73 (brs, 1H), 4.57 (m, 2H), 2.32 (s, 2H), 2.12 (s, 3H), 1.88 (d, J = 1.5 Hz, 3H), 1.57 (s, 3H), 0.98 (s, 3H); δ for minor isomer 12b: 5.84 (brs, 1H), 4.80 (m, 2H), 2.16 (s, 3H), 1.81 (d, J = 1.5 Hz, 3H), 1.49 (s, 3H), 1.10 (d, J = 6 Hz, 3H).

MS: m/e calcd. for $C_{18}H_{22}O_6$: 334.1399; found: 334.1425 (7), 218 (37), 123 (100), 122 (42), 94 (33), 91 (20), 79 (47), 77 (25), 55 (45).

3-Phenylthio-6,9,10-trimethyl-12-hydroxytricylco-[7.4.0.$0^{2,6}$]trideca-2,10-diene-4,8-dione (17) from the epoxides 11.

To a solution of 11 (275 mg) in dry THF (4 ml) was added 0.5 N 9-BBN in THF (2.2 ml). The solution was stirred at room temperature under nitrogen for 1.5 hr. The solvent was evaporated at reduced pressure and the resulting oil was dissolved in ether (8 ml). Ethanolamine (70 mg) was added and mixture was stirred at room temperature for 1 hr. The precipitated 9-BBN-ethanolamine complex was removed by centrifuging and the supernatant concentrated under reduced pressure to give the crude allylic alcohol 14 as an oil. To a solution of the crude 14 in ethanol (5 ml) was added benzenethiol (120 mg) and 2 N KOH (25 µl). After stirring under nitrogen for 8 hr at 0° a further 25 µl of 2 N KOH was added and the solution heated under reflux for 1.5 hr. The solution was poured onto sat. $NaHCO_3$ (20 ml), extracted with $CHCl_3$, dried ($NaSO_4$), and the solvent evaporated to give an oil which upon trituration with ether provided the crystalline 17 (200 mg) (mp 209-11).
IR (neat): 3420, 1705 cm^{-1}.
^{1}HMR ($CDCl_3$) δ: 7.29 (brs, 5H aromatic H's), 5.73 (brs, 1H, C-11 H), 4.10 (m, 1H, C-12 H), 3.62 (dd, J = 11, 4 Hz, 1H, C-1 H), 2.96 (d, J = 13 Hz, 1H) and 2.51

(d, J = 13 Hz, 1H) (C-7 H's), 2.56 (s, 2H, C-5 H's), 1.78 (d, J = 1.5 Hz, 3H, C-10 CH_3), 1.6 (m, 3H, C-13 H's and -OH), 1.35 (s, 3H) and 1.32 (s, 3H) (C-6,9 CH_3's).

MS: m/e calcd. for $C_{22}H_{24}O_3S$: 368.1449; found: 368.1444 (100), 350 (33), 335 (27), 285 (45), 284 (21), 199 (23), 198 (27), 185 (21), 175 (20), 109 (37), 91 (48), 77 (45), 65 (22).

^{13}CMR (DMSO-d_6) δ: 209.8 (s, C-8), 201.5 (s, C-4), 184.1 (s, C-2), 135.4 (s, C-1'), 133.9 (s) and 132.7 (s) (C-3, 10), 130.6 (d, C-11), 129.1 (d x2) and 128.1 (d x2) (C-2',3'), 126.3 (d, C-4'), 65.4 (d, C-12), 52.3 (t, C-7), 51.8 (s) and 49.1 (s) (C-6,9), 47.4 (d, C-1), 46.7 (t, C-5), 35.0 (C-13), 28.6 (q), 23.9 (q), and 19.6 (q) (C-6,9,10 CH_3's).

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